Antigen-specific active immunotherapy for ovarian cancer

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[Intervention Review]

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Ninke Leffers[1], Toos Daemen[2], Wijnand Helfrich[3], H Marike Boezen[4], Ben J Cohlen[5], Cornelis JM Melief[6], Hans W Nijman[2]

[1]Obstetrics & Gynecology CB30, University Medical Center Groningen, University of Groningen, Groningen, Netherlands. [2]University Medical Center Groningen, University of Groningen, Groningen, Netherlands. [3]Department of Surgery. Translational Surgical Oncology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands. [4]Unit Chronic Airway Diseases, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands. [5]Department of Obstetrics & Gynaecology, Isala Clinics, Location Sophia, Zwolle, Netherlands. [6]Department of Immunohaematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands

Contact address: Ninke Leffers, Obstetrics & Gynecology CB30, University Medical Center Groningen, University of Groningen, Hanzeplein 1, P.O. Box 30.001, Groningen, 9700 RB, Netherlands. n.leffers@umcg.nl.

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ABSTRACT

Background

Despite advances in chemotherapy, prognosis of ovarian cancer remains poor. Antigen-specific active immunotherapy aims to induce tumour-antigen-specific anti-tumour immune responses as an alternative treatment for ovarian cancer.

Objectives

To assess the feasibility of antigen-specific active immunotherapy for ovarian cancer. Primary outcomes are clinical efficacy and antigen-specific immunogenicity with carrier-specific immunogenicity and side effects as secondary outcomes.

Search methods

For the previous version of this review, a systematic search of the Cochrane Central Register of Controlled Trials (CENTRAL) 2009, Issue 3, Cochrane Gynaecological Cancer Group Specialized Register, MEDLINE and EMBASE databases and clinicaltrials.gov was performed (1966 to July 2009). We conducted handsearches of the proceedings of relevant annual meetings (1996 to July 2009).

For this update of the review the searches were extended to October 2013.

Selection criteria

Randomised controlled trials (RCTs), as well as non-randomised non-controlled studies that included participants with epithelial ovarian cancer, irrespective of stage of disease, and treated with antigen-specific active immunotherapy, irrespective of type of vaccine, antigen used, adjuvant used, route of vaccination, schedule, and reported clinical or immunological outcomes.

Data collection and analysis

Two reviews authors independently performed the data extraction. Risk of bias was evaluated for RCTs according to standard methodological procedures expected by The Cochrane Collabororation or for non-RCTs using a selection of quality domains deemed best applicable to the non-randomised non-controlled studies.

Main results

Fifty-five studies were included (representing 3051 women with epithelial ovarian cancer). Response definitions showed substantial variation between trials, which makes comparison of trial results unreliable. Information on adverse events was frequently limited. Furthermore, reports of both RCTs and non-RCTs frequently lacked the relevant information necessary to assess risk of bias. Serious biases in most of the included trials can therefore not be ruled out.

The largest body of evidence is currently available for CA-125 targeted antibody therapy (16 studies: 2339 participants). Non-RCTs of CA-125 targeted antibody therapy suggests increased survival in humoral and/or cellular responders. However, four large randomised placebo-controlled trials did not show any clinical benefit despite induction of immune responses in approximately 60% of participants.

Other small studies targeting many different tumour antigens showed promising immunological results. As these strategies have not yet been tested in RCTs, no reliable inferences about clinical efficacy can be made. Given the promising immunological results, limited side effects and toxicity exploration of clinical efficacy in large well-designed RCTs may be worthwhile.

Authors' conclusions

We conclude that despite promising immunological responses, no clinically effective antigen-specific active immunotherapy is yet available for ovarian cancer. Results should be interpreted cautiously as there was a significant lack of relevant information for the assessment of risk of bias in both RCTs and non-RCTs.

PLAIN LANGUAGE SUMMARY

Antigen-specific active immunotherapy for ovarian cancer

Background

Ovarian cancer is the leading cause of death from gynaecological cancers. Standard therapy consists of surgery and chemotherapy. Responses to chemotherapy are generally good, however, the majority of women will relapse, for which no curative treatment is available. The presence of certain immune cells in tumours is associated with longer survival. This suggests that stimulation of anti-tumour immune responses, i.e. immunotherapy, might be a useful approach to improve outcome for women with ovarian cancer.

Review question

In this review, the feasibility of antigen-specific active immunotherapy is evaluated. Antigen-specific active immunotherapy aims at the induction of anti-tumour immune responses through the administration of a tumour-antigen, a molecule that is expressed by tumour cells and hardly expressed by healthy cells. Information on clinical outcome, immunological responses, and side effects was collected.

Main findings

Fifty-five studies, which included 3051 women with ovarian cancer were identified, published between 1966 and 2013. The most frequently described strategy was administration of antibodies targeting the tumour antigen CA-125 (2339 participants in 16 studies). Most of these primarily evaluated safety and immunological responses. Severe flu-like and gastrointestinal symptoms occurred in 7% to 30% of participants. Antibodies and immune cells recognising the tumour antigen CA-125 were frequently detected, albeit response rates varied between studies. Despite these promising immunological responses, no survival advantage for participants treated with CA-125 directed antibody compared to placebo was found in four large studies.

For strategies not relying on antibody administration, similar conclusions cannot be drawn as immune system to the vaccine. Overall, treatment was well-tolerated, with inflammatory side effects at injection site most frequently reported. Responses of the immune system were observed for most strategies studied, but their clinical benefit still has to be evaluated in large trials.

Quality of the evidence and conclusions

Because there is currently no high-quality evidence of clinical benefit, antibody therapy targeting CA-125 should in its current form not be incorporated in standard treatment.

Based on a lack of uniformity in included studies, we strongly advocate universal adoption of response definitions, guidelines for adverse events reporting, and directives for trial conduct and reporting. Furthermore, results from ongoing RCTs are awaited and further RCTs should be conducted.

BACKGROUND

Description of the condition

Ovarian cancer is the sixth most common cancer and the seventh cause of death from cancer in women worldwide (Parkin 2006). It is the second most common gynaecological cancer and the leading cause of death from gynaecological cancers in the Western world. As the majority of ovarian malignancies (80% to 90%) arise from the epithelium, all statements in the remainder of this review about ovarian cancer apply to epithelial ovarian cancer only. Worldwide age-standardised incidence rates range from 2.6 per 100,000 in Northern Africa to 13.3 per 100,000 in Northern Europe (Parkin 2006).

Stage of disease at presentation is the most important prognostic factor. Due to the asymptomatic course of the disease, the majority of participants have extensive disease at presentation (stage III to IV according to FIGO classification (Benedet 2000)). Despite standard treatment, which consists of cytoreductive surgery and platinum-based chemotherapy, almost all women with advanced stage disease at presentation will relapse, with a median progression free survival (PFS) of only 18 months. When residual or recurrent disease manifests itself, resistance to chemotherapy often prohibits further curative therapy, resulting in a disease specific five-year survival for women with advanced stage ovarian disease of only 10% to 20% (Agarwal 2006; Thigpen 2000).

Description of the intervention

The immune system seems to play a role in ovarian cancer. This is reflected in the observation that in more than half of women with ovarian cancer, T- cells are present within tumour-islets (Raspollini 2005; Zhang 2003). Women with advanced ovarian cancer, whose tumour is infiltrated by these T-cells, have a better clinical outcome compared to women without these tumour-infiltrating T-cells (Dong 2006; Raspollini 2005; Zhang 2003). More specifically, higher numbers of cytotoxic T-cells, which can directly recognise and kill tumour cells, and increased ratios between cytotoxic T-cells ($CD8^+$) and helper T-cells ($CD4^+$) within the tumour epithelium are associated with improved survival (Sato 2005).

Immunotherapy is one of the novel therapeutic strategies under investigation for ovarian cancer. It aims to induce or enhance active immune responses directed towards the tumour and to consolidate anti-tumour effects of standard therapy, delay and possibly prevent progression of disease. More specifically, antigen-specific active immunotherapy aims at activation of the adaptive immune system directed towards a specific target antigen through administration of a molecular defined antigen-specific vaccine to the patient.

How the intervention might work

An antigen is a molecule, usually a protein or polysaccharide, which can stimulate an immune response. Tumour antigens can be subdivided into different categories such as mutated self proteins, products of oncogenes (e.g. Her-2/Neu), mutated tumour suppressor genes (e.g. p53), and aberrantly expressed self proteins (e.g. sperm protein 17, MAGE-1). Numerous tumour-associated antigens are known in ovarian cancer. To obtain a tumour-specific immune response, immunotherapy exploits the differential expression of antigens between normal and tumour cells. A major challenge concerning the safety of immunotherapy lies in the prevention of auto-immunity i.e. induction of immune cells that preferentially recognise and kill tumour cells, but avoid destruction of normal body cells. From a theoretical point of view, other possible side effects include allergic reactions to components of the vaccine and inflammatory reactions at the site of injection.

Why it is important to do this review

Several immunotherapeutic strategies are now being employed using different tumour antigens. These studies have, however, generally not yet evolved past phase I/II studies. To our knowledge, no systematic review of antigen-specific active immunotherapy in ovarian cancer has been carried out so far.

The immunogenicity and clinical efficacy of antigen-specific active immunotherapy in ovarian cancer is evaluated in this review. A systematic review about this topic is useful to ascertain the achievability of this treatment modality for ovarian cancer.

OBJECTIVES

The primary objective of this review was to assess the efficacy (i.e. clinical and/or immunological responses) of antigen-specific active immunotherapy for the treatment of ovarian cancer. The secondary objective was to establish which immunotherapeutic strategies combined with which tumour antigens provide the best immunological and clinical results.

METHODS

Criteria for considering studies for this review

Types of studies

We anticipated that there would be no randomised controlled trials (RCTs) on this subject. Therefore we also included phase I,

phase II non-randomised and non-controlled and if available phase III studies. We realised that results from non-randomised, non-controlled studies cannot readily be extrapolated to the general population. Nevertheless, we felt that given the anticipated lack of RCTs, inclusion of these studies into this review was justifiable.

Types of participants

Women diagnosed with epithelial ovarian cancer, irrespective of stage of disease. However, as patient populations may differ substantially between different types of studies to be included in this review, for each study we documented what type of person was included into the study (e.g. women with end-stage disease or women with residual disease).

Because we anticipated that there would not be many studies that included women with ovarian cancer only, we also included immunotherapeutic studies in people with cancer that included at least two women with ovarian cancer; with the additional requirement that the results for these individual women were separately identifiable from the study publication or communication with the author, and only data on these women were extracted for the review. We were fully aware of the vigilance necessary when drawing conclusions based on studies with such small numbers, but felt that given the anticipated lack of large RCTs, inclusion of these studies into this review was justifiable.

Types of interventions

Antigen-specific active immunotherapy is defined as therapy that aims at inducing an adaptive immune response directed towards the tumour by means of administration of a specific well-defined tumour antigen. We compared interventions with each other based on the above-mentioned characteristics.

We included all interventions that aimed at antigen-specific active immunotherapy irrespective of type of vaccine, antigen used, adjuvant used, route of vaccination, vaccination schedule.

Types of outcome measures

Primary outcomes

Clinical efficacy

To assess clinical efficacy we evaluated the following:

1. Tumour responses to immunotherapy (complete/partial response, stable/progressive disease), as measured by:
   - CA-125 levels according to or transposable to Gynecologic Cancer Intergroup (GCIG) criteria (Rustin 2004);
   - tumour response according to WHO criteria (WHO 1979) or Response Evaluation Criteria in Solid Tumors Group (RECIST) criteria (Therasse 2000).

2. If available, we evaluated responses to post-immunotherapy treatment, as there are indications that people with small cell lung cancer treated with chemotherapy after immunotherapy have increased survival as opposed to people who did not receive immunotherapy (Antonia 2006).

3. If available, survival differences based on treatment with immunotherapy.

Antigen-specific immunogenicity

We recorded the number of observed antigen-specific humoral and cellular responses. When possible, we separately reported responses of cytotoxic ($CD8^+$) T-lymphocytes and/or helper ($CD4^+$) T-lymphocytes.

Secondary outcomes

Carrier-specific immunogenicity

As certain immunotherapeutic strategies rely on the use of carriers that may be the subject of an immune response besides the intended antigen-specific immune response, we recorded information on the induction of carrier-specific immune responses when appropriate.

Adverse events

To obtain information on the toxicity of antigen-specific immunotherapy, we extracted data on adverse events observed and reported in the different studies. Adverse events were categorised as local adverse events at the site of immunisation or systemic adverse events (all other reported adverse events). Systemic adverse events were subdivided into autoimmunity, allergic reactions and other adverse events occurring after immunisation. If sufficient information was available, adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE 2009).

Search methods for identification of studies

For the original review (Leffers 2010), we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 9 (Appendix 1) and the Cochrane Gynaecological Cancer Group Specialized Register in October 2013. Furthermore, we also searched MEDLINE (1966 to July 2009) (Appendix 2) and EMBASE (1974 to July 2009) (Appendix 3) according to the search strategies listed, well as the prospective trial register www.clinicaltrials.gov.

Handsearcing was undertaken of abstracts in the proceedings of annual meetings of Society of Gynecologic Oncologists, the American Association for Cancer Research and the International Society for Biological Therapy of Cancer (1996 to July 2009). The

International Society for Biological Therapy of Cancer has been renamed the Society for Immunotherapy of Cancer (SITC), thus we also searched the proceedings of the annual meeting of SITC. For this update of the review the searches were extended up to October 2013.

The bibliography of each primary reference and of recent reviews of immunotherapy for ovarian cancer was checked for additional study publications. In addition, we wrote to specialists involved in research regarding immunotherapy for ovarian cancer for information about the results of unpublished or ongoing studies. Relevant data were included in this review.

There were no language restrictions other than those inherent to the databases surveyed.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to Reference Manager, duplicates were removed and two review authors (HWN and NL) independently examined the remaining references. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. Two review authors (HWN and NL) independently assessed the eligibility of retrieved papers. We resolved differences by discussion or by appeal to a third review author (TD) if necessary. We documented reasons for exclusion.

Data extraction and management

Two review authors (HWN and NL) independently extracted data on characteristics of participants and interventions, study quality and endpoints for included studies, onto a data extraction form specially developed for the review (Appendix 4).

Where data on clinical efficacy and antigen-specific immunogenicity were missing from reports, we attempted to contact the authors to obtain the missing information. A third review author (WH or TD) checked the results.

Assessment of risk of bias in included studies

We assessed the risk of bias in RCTs by means of The Cochrane Collaboration's 'Risk of bias' tool.

No standard tools to evaluate validity are available for non-RCTs. Instead, for these studies we evaluated the risk of bias using the following four domains (Table 1):

- sample definition and selection
  - clear definition of inclusion/exclusion criteria
  - representative selection
  - adequate description of baseline characteristics
- interventions:
  - clear specification
  - concurrent/concomitant treatment
- outcomes:
  - specifications of outcome measures
  - relevance of outcome measures
  - reporting of outcome measures
- statistical analysis:
  - adequate rationale for number of participants included
  - adequate description withdrawal/exclusion during the study
  - adequate presentation of results.

These domains were selected as representative for, and applicable to, non-randomised non-controlled studies from a list of 12 quality domains and items deemed to be pivotal to the assessment of non-RCTs (Deeks 2003).

Two review authors (HWN and NL) carried out the 'Risk of bias' assessment. We resolved any discrepancies by discussion; if necessary we consulted a third author (WH or TD).

Data synthesis

This review provides a narrative analysis, because the included studies are highly heterogenous regarding intervention and outcome measures. Furthermore, data in publications were often presented with insufficient details (lack of standard deviations (SDs) or only some of the multiple outcomes presented), and additional information from report authors was difficult to obtain. Therefore we felt that quantitative meta-analysis and calculation of effect size estimates would neither be meaningful nor appropriate in this review. We limited analysis to a structured summary and discussion of available studies and findings.

RESULTS

Description of studies

Results of the search

Initial version of review

From the electronic searches of MEDLINE and EMBASE, 56 out of 311 abstracts were selected as potentially compliant with the selection criteria and full texts were retrieved. Evaluation of the retrieved full texts resulted in the exclusion of 26 papers (see Excluded studies). In addition to the 30 selected full texts, another 14 abstracts were identified by handsearching the proceedings of the periodic meetings specified in the methods section. Study authors were contacted for manuscripts, but no full texts were obtained for these abstracts. Together the 44 selected full texts and

meeting abstracts described a total of 35 studies. Search of the prospective trial register www.clinicaltrials.gov resulted in identification of an additional 26 studies. For only four of these could a full text or meeting abstract be retrieved and only one study complied with our inclusion criteria (Sabbatini 2007). The remaining studies were either ongoing (n = 15) or completed but not yet published (n = 6). Search of CENTRAL (2009, Issue 3) did not identify any additional studies. Thus, a total of 36 studies were included in this review. Generally, the most recent peer-reviewed publication was selected as the primary reference.

First update of review

For the update of the review, the electronic searches of MEDLINE and EMBASE resulted in an additional 23 included papers and 10 excluded papers (Characteristics of excluded studies). For five studies in the previous version of this review, a full text publication, update or additional paper was now available. Search of CENTRAL (2013, Issue 3) did not yield any additional studies. Search of clinicaltrials.gov resulted in two additional published studies. Futhermore, 26 relevant studies without available results were identified (Characteristics of ongoing studies). Twelve studies are currently recruiting participants, four studies are ongoing but not recruiting, nine studies are classified as completed and for two studies status is unknown. Overall, an additional 19 studies were included in the update of this review resulting in a total number of 55 included studies involving 3051 women (Characteristics of included studies).

Included studies

The 55 studies included in this updated review were all published in English (Characteristics of included studies, Table 2).

Design

As we expected the majority of studies were uncontrolled phase I or II studies (43 out of 55). Only four studies were randomised placebo-controlled studies (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013). Randomised allocation of participants to different regimens was used in eight studies (Baumann 2011; Braly 2009; Chu 2012; Freedman 1998; Goh 2013; Heiss 2010; Method 2002; Sabbatini 2006). In four studies the immunogenicity of a previously applied immuno scintigraphic agent was retrospectively studied (Möbus 2003; Noujaim 2001; Schultes 1998; Wagner 1993).

Sample sizes

The median number of women with epithelial ovarian cancer treated per study was 20 (range 2 to 888). Nineteen studies included less than 10 participants. Seventeen studies also included participants with other types of cancer (Berinstein 2012; Brossart 2000; Dhodapkar 2012; Gribben 2005; Gulley 2008; Heiss 2010; Kaumaya 2009; Le 2012; Letsch 2011; Mohebtash 2011; Morse 2011; Odunsi 2012; Ohno 2009; Peethambaram 2009; Sandmaier 1999; Ströhlein 2009; Tsuda 2004). A sample size calculation or rationale was provided for 13 studies only (Baumann 2011; Berek 2004; Berek 2009; Braly 2009; Gribben 2005; Heiss 2010; Leffers 2009a; Rahma 2012; Sabbatini 2006; Sabbatini 2007; Sabbatini 2012; Sabbatini 2013; Vermeij 2012).

Participants

As was expected, the disease status at study entry varied largely between studies (Table 2). Participants with evidence of residual or recurrent disease after treatment were most frequently included (27 out of 55) (Baumann 2011; Brossart 2000; Ehlen 2005; Galanis 2010; Gordon 2004; Gribben 2005; Gulley 2008; Heiss 2010; Kaumaya 2009; Le 2012; Leffers 2009a; MacLean 1992; MacLean 1996; Möbus 2003; Mohebtash 2011; Nicholson 2004; Noujaim 2001; Peethambaram 2009; Ströhlein 2009; van Zanten-Przybysz 2002; Vermeij 2012).Six studies included participants with and without evidence of disease after prior therapy (Berinstein 2012; Braly 2009; Chianese-Bullock 2008; Odunsi 2007; Sabbatini 2006; Tsuda 2004). Fourteen studies included participants with complete response to therapy for primary or recurrent disease (Berek 2001; Berek 2004; Berek 2009; Chu 2012; Diefenbach 2008; Goh 2013; Imhof 2013; Morse 2011; Odunsi 2012; Rahma 2012; Sabbatini 2000; Sabbatini 2007; Sabbatini 2012; Sabbatini 2013). In one study, treatment was administered together with adjuvant chemotherapy after primary cytoreductive surgery (Braly 2009). For the remaining 14 studies disease status at entry was not reported (Berinstein 2013; Dhodapkar 2012; Freedman 1998; Letsch 2011; Ma 2002; Method 2002; Nishikawa 2006; Ohno 2009; Pfisterer 2006; Reinartz 2004; Sandmaier 1999; Schultes 1998; Takeuchi 2013; Wagner 1993).

Interventions

The majority of studies described antibody therapy (21 out of 55), usually targeting CA-125 (16 (2339 women) out of 21). Most studies included only one target antigen in the vaccine, but in 10 studies multiple antigens were simultaneously targeted (Berinstein 2012; Chianese-Bullock 2008; Chu 2012; Gulley 2008; Imhof 2013; Mohebtash 2011; Morse 2011; Sabbatini 2007; Takeuchi 2013; Tsuda 2004). Antibodies were usually administered intravenously (12 out of 21). For other vaccine types, subcutaneous injections were most common (21 out of 34).

Concurrent treatment with immunomodulatory drugs was not allowed in 15 out of 55 studies. In an additional 20 studies, concomitant immunomodulatory agents were not part of the studied intervention, but no explicit statements were made about prohibition of such drugs in the protocol. In 18 studies immunomodulatory drugs were part of the protocol (i.e. carboplatin-paclitaxel, cyclophosphamide, IL-2 +/- GM-CSF, TLR agonists poly-ICLC or resiquimod, or diphenhydramine) and one of these allowed interruption of immunotherapy by chemotherapy for progressive

disease (Reinartz 2004). Furthermore, two retrospective studies explicitly mentioned that concurrent chemotherapy was allowed at the discretion of the treating clinician (Möbus 2003; Wagner 1993).

Outcomes

Information on immunological responses, clinical responses, survival and adverse events was available for 51, 35, 37 and 45 studies respectively.

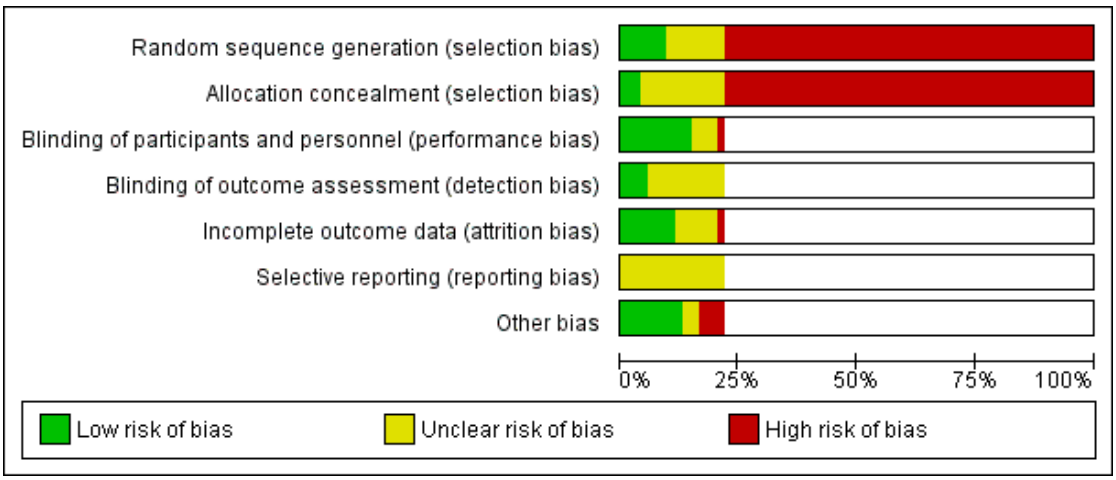
Excluded studies

A summary of the excluded studies is given in the table of Characteristics of excluded studies. Frequent reasons for exclusion were inclusion of too few participants with ovarian cancer and the impossibility to distinguish results of women with ovarian cancer from other study participants.

Risk of bias in included studies

We evaluated risk of bias using The Cochrane Collaboration's 'Risk of bias' tool. Results of individual studies (both RCT and non-RCT) are available in the table of Characteristics of included studies. For RCTs, assessment of risk of bias was hindered by the fact that for four of the 12 RCTs only meeting abstracts were available. The eight trials, for which we could retrieve full texts, also did not report on some of the items of the 'Risk of bias' tool. With this substantial lack of information, it is highly likely that included studies are subject to biases and difficult to make any statements about the validity of the included RCTs (Figure 1).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. The high risk of selection bias in the majority of included studies is a reflection of the high number of uncontrolled studies in this review. The risk of the remaining biases could not be adequately judged for the included uncontrolled studies, thus explaining the large percentage of missing risk assessments.



In addition to the 'Risk of bias' tool, we evaluated non-RCTs according to the checklist provided in Table 1. An overview of the results is provided in Table 3. Important observations from this table are the lack of clearly defined in-/exclusion criteria in 13 out of 43 studies combined with the serious under-reporting of baseline characteristics (29 out of 43 studies), which makes it impossible to evaluate whether the study populations were representative of the true population. Although the investigational interventions were well described in the majority of studies (39 out of 43), information on the allowance or application of concomitant immunomodulatory treatment was frequently absent (21 out of 43). Albeit a clear description of outcome measures was available for 29 studies, an adequate calculation of sample size based on a clearly defined primary outcome measure was available for only five studies. Furthermore, the applied checklist shows that the justification of withdrawals and exclusions during the study, as well as the presentation of study results are items that require serious

attention in the reports of these non-randomised studies.
Based on the above, the risk of bias in the studies included in this systematic review cannot be neglected. Especially selection bias (selection of a treatment population not comparable to control group or true population), attrition bias (inadequate reporting of withdrawal and exclusions during the study resulting in possible over- or underestimation of effect) and selective reporting bias are likely to affect the studies included in this review. The effects of interventions described below must therefore be interpreted with prudence.

Allocation

As can be deduced from the Characteristics of included studies table, we were unable to identify the method of randomisation and allocation for several randomised studies, which means that we cannot rule out a selection bias for these studies. For the remaining RCTs, selection bias does not seem likely.
The majority of included studies however were early phase non-randomised studies with only a single study arm. Selection bias in these studies may have occurred in several ways: 1) selective inclusion of patients with no other treatment options due to end-stage disease, at which point, function of the immune system may also be seriously impaired, thus resulting in an underestimation of immunogenicity and possible clinical benefit of a given vaccine, or 2) selective recruitment of fairly immunocompetent patients with no evidence of disease, resulting in a possible overestimation of immunogenicity and possible clinical benefit of a given vaccine.

Blinding

Inherent to the study design, no blinding of patients or treating (study) physicians was performed in any of the non-RCTs. All of the participants may have had benefit from the additional attention awarded to them as participants in a study, and performance bias may thus have influenced the results of these studies. Furthermore, it is unclear whether for these studies, outcome assessors were aware of the clinical condition of patients, thus detection bias may have occurred in these studies.
Blinding of participants, care givers and/or outcome assessors was described in four RCTs only, all comparing antibody therapy versus placebo (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013). The other RCTs compared dosage levels (Baumann 2011; Freedman 1998), administration route (Sabbatini 2006), number of gifts of a given drug (Method 2002), timing of the intervention in relation to standard chemotherapy (Braly 2009), addition of a immunomodulatory drug (Chu 2012), or immunotherapeutic intervention compared with standard of care (Goh 2013; Heiss 2010). Given these study designs, we feel that for most of these studies, the risk of performance bias is low. Information on blinding of outcome assessors was frequently missing. The risk of detection bias can therefore not be reliably judged.

Incomplete outcome data

Only one RCT was deemed to have a high risk of attrition bias based on the differences in withdrawals between groups (Heiss 2010). Risk of attrition bias was unclear for five other RCTs (Berek 2001; Freedman 1998; Goh 2013; Method 2002; Sabbatini 2006) and deemed low for the remaining RCTs (Baumann 2011; Berek 2004; Berek 2009; Braly 2009; Chu 2012; Sabbatini 2013).

Selective reporting

None of the included studies had a publicly available registered study protocol. It is therefore unclear whether studies selectively reported outcomes.

Other potential sources of bias

Given the elapsed time since publication of the meeting abstract, a publication bias is likely to exist for two out of three RCTs for which only a meeting abstract was available (Berek 2001; Freedman 1998). Study completion for the third RCT with only a meeting abstract available was expected at the end of 2013 (Goh 2013).

Effects of interventions

Primary outcomes

Clinical efficacy

Tumour responses

Clinical responses to therapy were evaluated in 34 studies (Table 4). In the reports on these studies, criteria for evaluation and/or explicit description of tumour responses per participant as well as the time point at which the evaluation took place were frequently not available. For studies that did mention evaluation of tumour responses, response outcomes were based on either CA-125 levels combined with tumour imaging (Baumann 2011; Chianese-Bullock 2008; Chu 2012; Diefenbach 2008; Ehlen 2005; Galanis 2010; Gordon 2004; Gulley 2008; Leffers 2009a; Ohno 2009; Rahma 2012; Sabbatini 2006; Ströhlein 2009; Tsuda 2004; van Zanten-Przybysz 2002; Vermeij 2012), CA-125 alone (Nicholson 2004; Wagner 1993) or imaging alone (Le 2012; Odunsi 2007; Peethambaram 2009; Reinartz 2004; Sabbatini 2012; Takeuchi 2013). Only 11 studies explicitly mentioned evaluation of imaging according to the internationally accepted WHO or RECIST criteria (Baumann 2011; Galanis 2010; Le 2012; Leffers 2009a; Ohno 2009; Rahma 2012; Reinartz 2004; Sabbatini 2012; Takeuchi 2013; Tsuda 2004; Vermeij 2012) and only five studies evaluated CA-125 levels according to GCIG

criteria or described CA-125 levels in such a way that evaluation according to these criteria was possible for at least some participants (Baumann 2011; Galanis 2010; Leffers 2009a; van Zanten-Przybysz 2002; Vermeij 2012). Strikingly, eight studies stated that evaluation of tumour responses was performed, but results could not be found in the publications (Diefenbach 2008; Dhodapkar 2012; Gulley 2008; Imhof 2013; Method 2002; Odunsi 2007; Reinartz 2004; Wagner 1993). Complete or partial tumour responses in participants with evidence of disease at study entry were reported by only four studies (Baumann 2011; Gordon 2004; Odunsi 2007; Takeuchi 2013) in a small fraction of participants. These results need to be interpreted with caution as criteria for response evaluation were not defined by two of these studies (Gordon 2004; Odunsi 2007).

Responses to 'secondary' treatment after immunotherapy

Although studies generally have a period of follow-up to obtain information on survival, in the majority of studies no report is given of subsequent treatment with and response to secondary chemotherapy. Nine studies mention that participants were treated with chemotherapy after immunotherapy (Berek 2004; Gordon 2004; Gribben 2005; Leffers 2009a; Möbus 2003; Odunsi 2007; Reinartz 2004; Ströhlein 2009; van Zanten-Przybysz 2002), but only four studies report response to secondary chemotherapy in relation to immunological responses to immunotherapy (Gordon 2004; Gribben 2005; Leffers 2009a; Reinartz 2004).

In a preliminary report, clinical responses of 28 out of 42 participants treated with chemotherapy for clinically relevant progression during or after antibody therapy were reported in conjunction with the induction of human-anti-mouse and anti-anti-idiotype antibodies. Although both participants with a complete response had strong humoral responses, similar or stronger antibody responses were also observed for participants with stable or progressive disease (Reinartz 2004). In another study, shortly after monotherapy with a monoclonal antibody, 13 out of 20 participants received chemotherapy combined with the monoclonal antibody. In this study, clinical responses to chemo-immunotherapy were only observed in participants with cellular responses to CA-125 and/or autologous tumour (Gordon 2004). A study of synthetic long peptides targeting p53 did not show any improvement of survival or tumour responses to secondary chemotherapy (Leffers 2009a). Finally, the authors of a study investigating plasmid DNA vaccination targeting CYP1B1 suggest that treatment has led to improved responses to third-line therapy, but no control group was included, nor do we find this observation convincing when solely taking the participants with ovarian cancer into account (Gribben 2005).

Survival

Definitions of survival used in the different studies varied greatly (Table 5 and Table 6). Furthermore, reliable statements about survival (dis)advantages can only be made based on RCTs. Only four studies were designed to primarily evaluate survival, however, no statistically significant differences in time to relapse and/or overall survival (OS) were found between participants treated with a monoclonal antibody or placebo (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013). Many non-RCTs also evaluated survival, frequently by comparing survival of participants with robust immunological responses to participants with no or weak immunological responses to treatment (Table 5 and Table 6). These results should be interpreted with great caution as shorter survival in non-responders could merely be a reflection of the general condition of these participants and well-known clinical and pathological prognostic parameters.

Antigen-specific immunogenicity

Humoral responses

Monoclonal antibodies may induce anti-idiotype antibodies (Ab2), directed primarily against the administered monoclonal antibody, as well as anti-anti-idiotype antibodies (Ab3) directed towards the target antigen. Anti-idiotype and anti-anti-idiotype antibodies were evaluated in 10 out of 21 studies respectively (Table 7 and Table 8). Response percentages varied greatly (Ab2: 3% to 100%, Ab3: 0% to 100%).

Fifteen studies of other vaccine types evaluated the induction of antigen-specific antibodies by ELISA, however only six studies clearly defined when an antibody titre or concentration was considered positive (Table 9) (Diefenbach 2008; Galanis 2010; Kaumaya 2009; Sabbatini 2007; Sabbatini 2012; Sandmaier 1999). Large differences in percentages of participants with measurable antigen-specific antibodies (IgG: 0% to 96%) existed. Possible explanations for these broad ranges are differences in 1) response definition, 2) number of treatment cycles after which humoral responses were measured and 3) targeted antigen.

Cellular responses

The induction of T-cells against the target antigen was investigated in 12 out of 21 monoclonal antibody studies (Table 10). The presence of antigen-specific T-cells was evaluated by commonly used tests, such as IFN-γ ELISPOT (Ehlen 2005; Gordon 2004; Method 2002; Sabbatini 2006), proliferation assay (Ma 2002; Noujaim 2001; van Zanten-Przybysz 2002), cytokine profiling (Noujaim 2001; Pfisterer 2006) and IFN-γ secretion assay (Ströhlein 2009). One study used the leukocyte migration inhibition assay (Wagner 1993), which nowadays is rarely used. Sabbatini 2013 will report the results regarding cellular responses in a separate not yet available publication. As described above for humoral responses, response definitions were frequently lacking

or inadequate. Nevertheless, cellular immunity against CA-125 was reported for 21% to 80% of participants. Antibody treatment targeting the membrane folate receptor however, did not induce cellular responses (van Zanten-Przybysz 2002). Recognition of autologous tumour cells by induced T-cells was determined in two studies only, with positive responses in five out of eight and one out of two participants respectively (Gordon 2004; Ströhlein 2009).
Antigen-specific cellular immune responses were evaluated for 26 out of 34 studies using other vaccine types (Table 11). The most frequently used assay was the IFN-γ ELISPOT assay, which was sometimes used to separately analyse $CD4^+$ and/or $CD8^+$ cells. Again, response definitions for positive and/or vaccine-induced responses were frequently absent or unclear (12 out of 34). In four of six studies targeting NY-ESO-1, antigen-specific T-cells were induced, with percentages of participants with NY-ESO-1-specific $CD8^+$ ranging from 33% to 92% (Dhodapkar 2012; Diefenbach 2008; Nishikawa 2006; Odunsi 2007; Odunsi 2012; Sabbatini 2012); one study did not report the results separately for ovarian cancer participants (Dhodapkar 2012). After treatment with vaccines targeting p53, p53-specific T-cells were observed in 64% to 100% of participants, irrespective of type of vaccine (Leffers 2009a; Rahma 2012; Vermeij 2012). Lastly, studies targeting multiple antigens demonstrated antigen-specific cellular immunity with varying immunogenicity of the different antigens targeted (Berinstein 2012; Brossart 2000; Chianese-Bullock 2008; Chu 2012; Mohebtash 2011; Morse 2011; Tsuda 2004).

Secondary outcomes

Carrier-specific immunogenicity

The majority of studies using a monoclonal antibody (17 out of 21) used a murine antibody, two studies used a trifunctional rat-mouse hybrid (Baumann 2011; Heiss 2010), and one study used a chimeric antibody construct (van Zanten-Przybysz 2002). Next to antigen-specific immunity, the induction of human-anti-mouse antibodies (HAMA) using HAMA-specific ELISA assays was assessed in 16 studies (Table 12). HAMA were present in 4% to 97% of participants immunised (Baumann 2011; Berek 2004; Braly 2009; Ehlen 2005; Gordon 2004; Method 2002; Möbus 2003; Pfisterer 2006; Reinartz 2004; Sabbatini 2006; Schultes 1998). It seems that the large variation between studies cannot be attributed to differences in dosage, but is best ascribed to different definitions of a HAMA response i.e. some studies only report robust responses, whereas others report all responses above a certain threshold. Furthermore, the point in time at which HAMA titres were measured is of importance as responses increase in frequency and strength with repeated administrations of the antibody (Baumann 2011; Gordon 2004; Method 2002; Möbus 2003).
Although six studies investigated synthetic carbohydrate antigens conjugated to the keyhole limpet haemocyanin (KLH) carrier protein (Freedman 1998; MacLean 1992; MacLean 1996; Sabbatini 2000; Sandmaier 1999; Sabbatini 2007), only one study reported on KLH-specific immunity (Sandmaier 1999). In this study, proliferative responses to stimulation with KLH and the KLH-antigen complex were substantially stronger than responses to the synthetic carbohydrate itself in all women with ovarian cancer tested, similar to what has previously been reported for viral vectors.
The use of recombinant viruses or bacteria as vectors was reported by five studies (Galanis 2010; Gulley 2008; Le 2012; Mohebtash 2011; Odunsi 2012). Anti-vector immune responses were reported to be investigated in three of these. In a study using a recombinant pox-virus, anti-vector immunity was induced in all participants with ovarian cancer (Gulley 2008). A study using a recombinant measles virus did not show any differences in anti-measles-antibody titres, but included participants were required to be immune to measles virus as part of the inclusion criteria (Galanis 2010). The use of live-attenuated listeria did result in virus-specific T-cells in some cancer participants, however, too few participants with ovarian cancer were tested to draw a conclusion for this specific disease entity (Le 2012).

Adverse events

For this review, adverse events were defined as any adverse change in health or side effect that occurred in a person who participated in the clinical study receiving the treatment, irrespective of whether the event could be attributed to the treatment received.
Although 45 studies mentioned adverse events, sufficiently detailed information on adverse events occurring during the study was available for only 36 out of 55 studies. Local adverse events were explicitly mentioned for 28 studies, all of which used local administration of the vaccine (i.e. intradermal, intramuscular or subcutaneous injection). When local adverse events were further specified, these were best summarised as pain at the injection site and local inflammatory responses (erythema, induration, pruritis). Ulceration and/or abscesses at the injection site were observed in nine of 89 participants with varying types of cancer participating in four studies (Freedman 1998; Berinstein 2012; Berinstein 2013; Gribben 2005) .
Systemic adverse events occurred in 35 studies and were explicitly reported not to have occurred in four studies. For the remaining six studies, no information on systemic adverse events could be deduced from the manuscript. Autoimmunity was explicitly reported by two studies. In one study, a participant with strong immunological responses to the vaccine developed a symptomatic hypothyroidism necessitating replacement therapy (Diefenbach 2008). A minor induction of anti-nuclear antibodies (grade I according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Trotti 2003)) was described for two participants receiving a multi-peptide vaccine (Chianese-Bullock 2008). Allergic reactions were described for a total of 14 participants (Berek 2009; Braly 2009; Ehlen 2005; MacLean 1992; Möbus 2003;

Pfisterer 2006; Ströhlein 2009). Allergic reactions were mild and easily managed, e.g. hypersensitivity, allergic exanthema, and urticaria. When study treatment was continued, this did not result in renewed allergic reactions (Braly 2009; Ehlen 2005; Möbus 2003; Pfisterer 2006).

Other systemic adverse events reported, irrespective of whether attributable to the investigated drug, included haematologic changes (e.g. anaemia, leucopenia), flu-like symptoms (including fatigue, myalgia, arthralgia, headache, fever and chills) and gastrointestinal events (e.g. nausea, vomiting, diarrhoea, and abdominal pain), most of which were classified as grade I or II events. Serious (CTC grade III or IV) adverse events were reported by 28 studies and varied from recurrent or progressive disease to local ulceration at injection site, and from abdominal pain and fever to elevated liver enzymes. In 17 studies, no serious adverse events were reported. Ten studies did not mention lack or presence of serious adverse events.

DISCUSSION

The aim of this review was to evaluate clinical and immunological efficacy of antigen-specific active immunotherapy in ovarian cancer, whilst also obtaining an impression of safety and tolerability of this treatment modality. The antigen-specific active immunotherapy described in this review can largely be divided into two strategies: (1) the administration of antibodies targeting a specific tumour antigen and (2) the administration of, or parts of, a specific tumour antigen itself. As expected, most studies were non-RCTs.

Antigen-specific humoral and/or cellular immunogenicity of the different interventions showed great variation for both monoclonal antibody studies and studies using other strategies. This variation may at least be partially attributed to the variation in immunological response definitions used by the different studies. It is therefore not possible to reliably compare studies and infer which intervention and/or immunisation strategy is most promising for the induction of strong anti-tumour immunity. Furthermore, only two studies evaluated recognition of autologous tumour cells in vitro and none evaluated immune responses at the tumour site. Although obtaining autologous tumour material may be burdensome, such assays would be extremely valuable as they comprise true interactions between induced immunity and tumour cells and could as such provide important information on how to continue improvement of immunotherapeutic strategies to reach clinical effectiveness.

Clinical responses to immunotherapy (i.e. tumour responses, responses to secondary treatment and survival benefits) were observed only incidentally and when described reliability of results was questionable due to the absence of clear response definitions. Furthermore, for studies in which a monoclonal antibody targeting CA-125 was used, the use of CA-125 as a marker for clinical response is questionable. An additional important comment regarding the likelihood of clinical responses to immunotherapy, especially in uncontrolled studies, which frequently include participants with recurrent disease, is the fact that this likelihood may be affected by the disease status at start of treatment (Leffers 2009). The indication for immunotherapeutic treatment in the adjuvant setting is supported by the observation of enhanced antigen-specific responses to immunotherapy when combined with chemotherapeutic agents currently or previously used in the primary treatment of ovarian cancer i.e. docetaxel or cyclophosphamide (Garnett 2008; Laheru 2008). Four large RCTs using a monoclonal CA-125 antibody in the adjuvant setting after successful primary therapy however did not demonstrate any differences in time to relapse and/or OS between the treatment and placebo arm (Berek 2001; Berek 2004; Berek 2009; Sabbatini 2013), which indicates that despite immunogenicity, CA-125 targeted monoclonal antibody therapy is clinically ineffective. For the studies of other vaccine types, no such conclusions can be made at this time as large RCTs and more studies in the adjuvant, rather than recurrent setting have yet to be performed for the different strategies.

Adverse events, reported in sufficient detail for interpretation, were reported in 65% of studies. A distinction was made between local and systemic events. The latter were further subdivided in autoimmunity, allergy and other adverse events. We did not evaluate whether adverse events could be or were considered attributable to the treatment studied, although for local adverse events this is indisputably the case. Inflammatory reactions and pain at the injection site were frequently reported for studies using intradermal, subcutaneous or intramuscular application, with ulceration at the most severe side of the spectrum. Severe or life-threatening systemic adverse events occurred in 62% of studies explicitly describing the occurrence or lack of severe adverse events. For monoclonal antibody studies, no pattern suggestive of a underlying treatment-associated process could be identified and events were often considered to be associated with ovarian cancer progression.

A disturbing observation regarding adverse events is the lack of uniformity in adverse event reporting. Reporting of safety and tolerability of new treatment strategies should have high priority in all studies of investigational drugs, especially in uncontrolled phase I and II studies. To promote uniformity in adverse event evaluation and reporting as well as the comparability of adverse events between studies, in addition to the NCI CTCAE (Trotti 2003), the Brighton Collaboration (Brighton Collaboration 2009) has committed itself to develop standardised, widely disseminated and globally accepted case definitions for an exhaustive number of adverse events following immunisation as well as guidelines for data collection, analysis, and presentation. These case-definitions and guidelines are freely available and we strongly recommend that, where applicable, these are used for all immunotherapeutic studies.

Interestingly, for 10 studies described in this review, information

from the study was collected from a meeting abstract only and often this meeting abstract was several years old. The lack of full text manuscripts, even after contacting abstract authors, strongly suggests the existence of a publication bias. To avoid the disappearance of negative studies, registration of trials in a prospective trial register is widely recommended and supported by the International Committee of Medical Journal Editors (ICMJE). However, initially in 2005 registration was only requested for RCTs. Since July 1, 2008 all trials prospectively assigning human participants to one or more health-related interventions to evaluate the effects on health outcomes are required to be registered in a clinical trial register approved by the WHO. From the ongoing studies section it is however apparent that despite registration in a prospective trial register, studies may suffer from publication bias as several relatively small studies started more than five years ago have not yet been published to date or closed according to the trial register. In addition to registration in trial registers, the uniform requirements for manuscripts submitted to biomedical journals drafted by the ICMJE encourage uniformity in reporting of clinical trials by stating ethical principles in conduct and reporting of research as well as proving recommendations relating to specific elements of editing and writing. As is obvious from this review, the scientific community might benefit substantially if also early phase uncontrolled clinically trials would strive for uniformity in trial conduct and reporting.

This review also emphasises another aspect of immunotherapeutic studies that warrants serious attention in the immunotherapeutic scientific community i.e. the lack of consensus on 1) what assays to use to establish immunogenicity of an intervention (Britten 2008), 2) what cut-offs to use to define true immunological responses and 3) response definitions for clinical efficacy. Given these large inconsistencies, it is evident that the elucidation of what type of immunological response is necessary for and/or a surrogate marker of clinical activity of an immunotherapeutic intervention is burdensome.

In summary, this review describes 55 immunotherapy studies including 3051 women with ovarian cancer. The most striking observations of this review unfortunately do not concern the aim of the review, but address the lack of uniformity in conduct and reporting of early phase immunotherapy studies. When temporarily discarding this methodological heterogeneity, it seems that although all strategies described are capable of inducing immunological responses, be it humoral or cellular, clinically effectiveness has thus far not been convincingly demonstrated. The largest body of evidence is available for CA-125 directed antibody therapy, which has been studied in 2339 people participating in 16 studies. As complete or partial clinical responses were reported in only one study and four large RCTs did not demonstrate any clinical benefit of antibody treatment, we feel that it is unlikely that clinical effectiveness of CA-125 directed antibody therapy for ovarian cancer will ever be obtained. However, in view of the immunological responses to and the usually mild side effects, we feel that further investigation of other antigen-specific active immunotherapy strategies in ovarian cancer is worthwhile.

AUTHORS' CONCLUSIONS

Implications for practice

At this point in time, there is no evidence of effective immunotherapy for ovarian cancer. Although promising immunological responses have been observed for most strategies evaluated, these do not coincide with clinical benefits for women with ovarian cancer. Furthermore, there are currently no immunological surrogate markers that correlate with clinical outcomes. Until evidence of true clinical effectiveness is available, immunotherapy should therefore not be offered as an alternative to standard therapy for primary or recurrent ovarian cancer.

Implications for research

Our primary recommendation relates to the necessity of uniformity in trial conduct and reporting. Not until universally accepted immunological and clinical response definitions and guidelines for adverse events reporting are adopted in immunotherapeutic studies, will it be possible to make any inferences about the achievability of immunotherapy as a treatment for ovarian cancer. Furthermore, expanding evaluation of immunogenicity to include recognition of autologous tumour is advisable. Given the usually mild side effects and the immunological responses witnessed in most studies, we feel that further investigation of antigen-specific active immunotherapy other than CA-125 targeted antibody therapy in ovarian cancer in randomised controlled trials is worthwhile.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baumann 2011

Methods	Randomised controlled phase II trial
Participants	45 ovarian cancer patients with evidence of disease after first- or second-line chemotherapy
Interventions	Intraperitoneal trifunctional bispecific antibody (catumaxomab - EpCAM): low dose (10-10-10-10 μg) versus high dose (10-20-50-100 μg)
Outcomes	Tumour responses Survival (progression free survival/overall survival) Immune responses: humoral (HAMA) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	Not explicitly stipulated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient data to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Study protocol not publicly available
Other bias	Low risk	

Berek 2001

Methods	Randomised placebo-controlled trial
Participants	252 stage III/IV ovarian cancer patients after successful primary surgery and chemotherapy
Interventions	Intravenous monoclonal antibody (oregovomab - CA125) versus placebo
Outcomes	Survival (time to relapse) Immune responses: humoral (Ab2, HAMA)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk', only abstract available
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Other bias	High risk	Possible publication bias

Berek 2004

Methods	Randomised placebo-controlled phase II Trial
Participants	145 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab) versus placebo

Berek 2004 (*Continued*)

Outcomes	Survival (time to relapse/overall survival) Immune responses: humoral (Ab2, HAMA) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Low risk	

Berek 2009

Methods	Randomised placebo-controlled phase III trial
Participants	371 stage III/IV ovarian cancer patients with complete clinical response to primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab) versus placebo
Outcomes	Survival (time to relapse) Immune responses Adverse events
Notes	

Berek 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised randomisation procedure
Allocation concealment (selection bias)	Low risk	Centralised randomisation procedure
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded to treatment assignment, post-randomisation immune responses and CA125 measurements
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded to treatment assignment, post-randomisation immune responses and CA125 measurements
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Low risk	

Berinstein 2012

Methods	Uncontrolled phase I study
Participants	23 late stage cancer HLA-A2^{+} participants with complete or partial response to primary therapy (ovarian cancer n = 6)
Interventions	Subcutaneous 7 short peptides (topoisomerase IIα, integrin β8 subunit precursor, ABI-binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31) Adjuvant: DepoVax
Outcomes	Survival (time to progression) Tumour response Adverse events
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Berinstein 2012 (*Continued*)

Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Berinstein 2013

Methods	Uncontrolled phase I study	
Participants	19 women with ovarian cancer with unknown disease status	
Interventions	Subcutaneous peptides (survivin) Adjuvant: DepoVax	
Outcomes	Immune responses (cellular) Adverse events	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Braly 2009

Methods	Randomised controlled phase II Trial	
Participants	40 stage III/IV ovarian cancer patients after primary debulking surgery with or without residual disease	
Interventions	Intravenous monoclonal antibody (oregovomab - CA125): concurrent (SIM) or delayed (OWD) with standard carboplatin/paclitaxel primary chemotherapy	
Outcomes	Survival (progression-free survival) Clinical responses Immune responses Adverse events	
Notes		

Risk of bias

Braly 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Low risk	

Brossart 2000

Methods	Uncontrolled phase I/II study
Participants	10 participants with measurable residual or recurrent breast or ovarian cancer (3 women with ovarian cancer)
Interventions	Subcutaneous peptide pulsed Dendritic Cells (n = 1: Her-2/Neu; n = 2 MUC-1)
Outcomes	Tumour responses Immune response Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Chianese-Bullock 2008

Methods	Uncontrolled phase I study
Participants	9 women with ovarian cancer with or without residual or recurrent disease after primary therapy
Interventions	Subcutaneous & intradermal multi peptide vaccine (FBP, Her-2/Neu & MAGE-A1) Adjuvant: Montanide ISA-51, GM-CSF
Outcomes	Tumour responses Immune response Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Chu 2012

Methods	Randomised controlled phase I/II study
Participants	14 ovarian cancer patients with complete clinical response to primary therapy (10 received treatment so far)
Interventions	Intradermal peptide pulsed Dendritic Cells (Her-2/Neu, hTERT, PADRE): vaccine alone versus single dose of cyclophosphamide prior to first vaccination
Outcomes	Tumour responses Immune response Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'

Chu 2012 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	High risk	Early termination due to financial limitations.

Dhodapkar 2012

Methods	Uncontrolled phase I study
Participants	45 participants with advanced malignancies, exact disease status unknown (ovarian cancer n = 6)
Interventions	Fusion protein of full length tumour antigen and human monoclonal antibody specific for DEC-205 Adjuvants: TLR agonist resiquimod and/or Poly-ICLC
Outcomes	Immune responses (cellular and humoral) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Diefenbach 2008

Methods	Uncontrolled phase I study
Participants	9 participants with ovarian cancer with complete clinical response to primary therapy
Interventions	Subcutaneous short peptide (NY-ESO-1) Adjuvant: Montanide ISA-51
Outcomes	Survival (time to progression) Tumour responses Immune responses: cellular and humoral Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Ehlen 2005

Methods	Uncontrolled phase II study
Participants	13 women with ovarian cancer with measurable recurrent disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (time to progression/survival) Tumour responses Immune responses: humoral (Ab2, Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Freedman 1998

Methods	Randomised controlled phase II study
Participants	30 ovarian cancer patients previously treated with platinum-based chemotherapy (disease status at study entry not described)
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) at two different dosages Adjuvant: detox B
Outcomes	Survival (progression free interval/survival) Tumour responses Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk', only abstract available
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk', only abstract available
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Other bias	High risk	Possible publication bias

Galanis 2010

Methods	Uncontrolled phase I study
Participants	21 ovarian cancer patients with persistent, recurrent or progressive disease after primary therapy
Interventions	Intraperitoneal recombinant measles virus (CEA)
Outcomes	Tumour responses Immune responses (humoral) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Goh 2013

Methods	Randomised controlled phase IIb trial
Participants	63 patients in complete remission after primary therapy
Interventions	Protein-pulsed dendritic cells (MUC1) versus standard of care
Outcomes	Survival Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk', only abstract available
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available

Goh 2013 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk', only abstract available
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Other bias	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available; study recently completed

Gordon 2004

Methods	Uncontrolled phase II study
Participants	20 ovarian cancer patients with recurrent disease
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (time to progression/survival) Tumour responses Immune responses: humoral (Ab2, Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Gribben 2005

Methods	Uncontrolled phase I study
Participants	17 participants with advanced cancer with progressive disease (ovarian cancer n = 6)
Interventions	Intramuscular plasmid DNA vaccine (CYP1B1)
Outcomes	Tumour responses Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Gulley 2008

Methods	Uncontrolled phase I/II study
Participants	25 participants with CEA or MUC1 over-expressing metastatic cancer with progressive disease following standard chemotherapy (ovarian cancer n = 3)
Interventions	Subcutaneous recombinant pox virus (CEA, MUC1): 1x vaccinia, ≥ 4 fowlpox Adjuvant: local GM-CSF
Outcomes	Survival (progression free survival/overall survival) Immune responses: cellular, humoral Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Heiss 2010

Methods	Randomised controlled open-label phase II/III trial
Participants	258 patients with malignant ascites due to epithelial cancer (ovarian cancer n = 129)
Interventions	Intraperitoneal trifunctional antibody (EpCAM) + paracentesis versus paracentesis
Outcomes	Survival (puncture-free survival/overall survival) Immune responses (HAMA) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Low risk	

Imhof 2013

Methods	Uncontrolled phase I study	
Participants	15 participants with complete remission after primary therapy	
Interventions	Intradermal dendritic cells pulsed with mRNA (TERT) and short peptide (Survivin)	
Outcomes	Immune responses (cellular) Adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Kaumaya 2009

Methods	Uncontrolled phase I study	
Participants	24 participants with metastatic and/or recurrent solid tumours (ovarian cancer n = 5)	
Interventions	Intramuscular synthetic long peptides (Her2) Adjuvant: Montanide ISA720	
Outcomes	Tumour responses Immune responses (humoral) Adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Le 2012

Methods	Uncontrolled phase I study
Participants	17 participants with advanced cancers after prior therapy (ovarian cancer n = 2)
Interventions	Intravenous recombinant listeria (mesothelin)
Outcomes	Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Leffers 2009a

Methods	Uncontrolled phase II study
Participants	20 women with epithelial ovarian cancer with (biochemical) recurrence not (yet) eligible for renewed chemotherapy
Interventions	Subcutaneous synthetic long peptides (p53) Adjuvant: Montanide ISA51
Outcomes	Survival (disease specific survival) Tumour responses Immune responses: humoral, cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Letsch 2011

Methods	Uncontrolled study
Participants	18 participants with WT1 expressing solid tumours (disease status unreported) (ovarian cancer n = 8)
Interventions	Short peptide (WT1) Adjuvant: KLH, GM-CSF
Outcomes	Tumour responses Immune responses (cellular) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Ma 2002

Methods	Uncontrolled study
Participants	4 women with ovarian cancer (disease status at study entry not described)
Interventions	Monoclonal antibody (MJ01- CA125)
Outcomes	Immune response: cellular
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

MacLean 1992

Methods	Uncontrolled phase I study	
Participants	10 women with ovarian cancer and residual or recurrent disease	
Interventions	Subcutaneous KLH conjugate (Thomson Friedenreich) Adjuvant: detox B	
Outcomes	Tumour responses Immune responses: humoral Adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

MacLean 1996

Methods	Uncontrolled phase II study	
Participants	34 women with ovarian cancer and evaluable residual or recurrent disease	
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) Adjuvant: detox B	
Outcomes	Survival (trial entry to death) Immune response: humoral	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Method 2002

Methods	Randomised controlled Study
Participants	102 women with ovarian cancer after primary therapy (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody (oregovomab - CA125): 2 gifts versus 3 gifts, versus 6 gifts
Outcomes	Tumour responses Immune response: humoral (Ab2, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk', only abstract available
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk', only abstract available
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available
Other bias	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk', only abstract available

Mohebtash 2011

Methods	Uncontrolled study
Participants	31 metastatic ovarian and breast cancer patients (ovarian cancer n = 14)
Interventions	Subcutaneous recombinant pox virus (MUC1 and CEA) Adjuvant: local GM-CSF
Outcomes	Survival: median time to progression 2 months (range 1-36) Immune responses (cellular) Adverse events: no severe adverse events, mostly locoregional grade 1 or 2 reactions
Notes	max. 3 patients overlap with Gulley 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Morse 2011

Methods	Uncontrolled phase I study
Participants	15 ovarian and breast cancer patients with no evidence of disease after prior therapy (ovarian cancer n = 8)
Interventions	Intradermal and subcutaneous short peptides in two groups (Group 1: APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I; Group 2: topoisomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1) Adjuvant: Montanide ISA-51, GM-CSF
Outcomes	Survival Immune responses: cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Möbus 2003

Methods	Retrospective uncontrolled study
Participants	44 ovarian cancer patients with clinical recurrence after primary therapy
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (time first dose to death/overall survival) Immune response: humoral (Ab2, Ab3, HAMA) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Nicholson 2004

Methods	Uncontrolled phase I study
Participants	26 epithelial ovarian cancer patients with residual disease (n = 19), microscopic disease (n = 3) after chemotherapy or 2nd complete remission (n = 4)
Interventions	Monoclonal antibody (HMFG1 - Muc1); first gift intraperitoneal (n = 16) or intravenous (n = 10), then id boosts Adjuvant: aluminium hydroxide
Outcomes	Tumour responses Immune response: humoral (Ab2) Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Nishikawa 2006

Methods	Uncontrolled phase II study
Participants	4 epithelial ovarian cancer patients after primary debulking surgery (disease status at study entry not described)
Interventions	Short peptide (NY-ESO-1) Adjuvant: incomplete Freund's adjuvant
Outcomes	Immune responses: cellular
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Noujaim 2001

Methods	Retrospective uncontrolled study
Participants	184 ovarian cancer patients with clinically or radiologically suspected recurrence
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)
Outcomes	Survival (overall survival) Immune responses: humoral (Ab3), cellular
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Odunsi 2007

Methods	Uncontrolled phase I study
Participants	18 ovarian cancer patients after chemotherapy for primary or recurrent disease with or without residual disease
Interventions	Subcutaneous short peptide (NY-ESO-1) Adjuvant: incomplete Freund's adjuvant
Outcomes	Survival: median time to progression 19.0 months Tumour responses: 1x CR, 17x unknown Immune responses: humoral, cellular Adverse events: well-tolerated, no further description
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Odunsi 2012

Methods	Uncontrolled phase I/II study
Participants	22 women with ovarian cancer without evidence of disease after primary therapy
Interventions	intradermal recombinant virus (NY-ESO-1); 1x vaccinia virus, 6x fowlpox boost
Outcomes	Survival (disease free survival) Immune responses: humoral, cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Ohno 2009

Methods	Uncontrolled phase II study	
Participants	12 patients with gynaecological malignancies resistant to standard therapy (ovarian cancer n = 6)	
Interventions	Intradermal short peptide (WT1) Adjuvant: Montanide ISA-51	
Outcomes	Tumour responses	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Peethambaram 2009

Methods	Uncontrolled phase I study	
Participants	18 patients with refractory metastatic tumours (ovarian cancer n = 4)	
Interventions	Intravenous recombinant fusion antigen pulsed antigen presenting cells (Her-2/neu) Adjuvant: GM-CSF (included in the recombinant fusion product)	
Outcomes	Survival (time to progression) Tumour responses Immune responses: cellular Adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Pfisterer 2006

Methods	Uncontrolled phase I study
Participants	36 Stage I-IV ovarian cancer patients within 6 weeks after completion of chemotherapy for recurrent disease (disease status at study entry not described)
Interventions	Subcutaneous monoclonal antibody (abagovomab - CA125)
Outcomes	Immune responses: humoral (Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Rahma 2012

Methods	Uncontrolled phase II study
Participants	21 ovarian cancer patients without evidence of disease after prior therapy
Interventions	Subcutaneous short peptide (p53) versus intravenous peptide-pulsed dendritic cells (p53) Adjuvant: Montanide ISA-51 and GM-CSF (only in cohort-treated with peptide)
Outcomes	Survival (progression-free survival, overall survival) Tumour responses Immune responses: cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Reinartz 2004

Methods	Uncontrolled multicentre phase Ib/II study
Participants	119 patients with ovarian cancer after at least primary treatment (disease status at entry not described)
Interventions	Intramuscular monoclonal antibody (ACA125 - CA125)
Outcomes	Survival (time first dose to death) Tumour responses Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Sabbatini 2000

Methods	Uncontrolled phase I study
Participants	25 ovarian cancer patients with complete clinical response to chemotherapy after residual or recurrent disease following primary therapy
Interventions	Subcutaneous KLH conjugate (LewisY penta saccharide - MUC-1) Adjuvant: QS-21
Outcomes	Survival (time to progression) Immune responses: humoral Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Sabbatini 2006

Methods	Randomised, open-label multicentre phase I study
Participants	42 stage II-IV ovarian cancer patients after chemotherapy for recurrence of disease with complete clinical response or measurable disease (< 2 cm)
Interventions	Intramuscular (im) or subcutaneous (sc) monoclonal antibody (abagovomab - CA125): 4 cohorts (2x im; 2x sc; 0.2 mg or 2 mg)
Outcomes	Survival (time to progression) Tumour responses Immune response: humoral (Ab3, HAMA), cellular Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Standard 2x2 factorial design
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk'
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Low risk	

Sabbatini 2007

Methods	Uncontrolled phase I/II study
Participants	11 epithelial ovarian cancer patients with complete clinical remission after primary therapy or chemotherapy for recurrent disease
Interventions	Subcutaneous heptavalent KLH conjugate (GM2, Globo-H, Lewis Y, Tn-MUC1, Tn (c) sTN(c), TF(c))
Outcomes	Survival (time to treatment failure) Immune responses: humoral
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Sabbatini 2012

Methods	Uncontrolled phase I study
Participants	28 ovarian cancer patients in second or third remission
Interventions	Subcutaneous overlapping long peptides (NY-ESO-1) Adjuvant: cohort 1 - no (n = 4); cohort 2: Montanide ISA-51 (n = 13); cohort 3: poly-ICLC in Montanide ISA-51 (n = 11)
Outcomes	Survival (time to progression) Tumour responses Immune responses: cellular and humoral Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Sabbatini 2013

Methods	Randomised placebo-controlled trial
Participants	888 ovarian cancer patients in complete clinical remission after primary therapy
Interventions	Subcutaneous monoclonal antibody (abagovomab - CA125)
Outcomes	Survival (recurrence free survival, overall survival) Immune responses: humoral (Ab3, HAMA), cellular (to be reported in separate paper) Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised randomisation
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'
Other bias	Low risk	

Sandmaier 1999

Methods	Uncontrolled phase II study
Participants	40 breast or ovarian cancer (n = 7) patients who underwent high-dose chemotherapy and autologous or syngeic stem cell rescue (disease status at study entry unknown)
Interventions	Subcutaneous KLH conjugate (Sialyl-Tn) Adjuvant: detox B

Sandmaier 1999 (*Continued*)

Outcomes	Immune responses: humoral, cellular	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Schultes 1998

Methods	Retrospective uncontrolled study	
Participants	75 stage I-IV ovarian cancer patients (disease status at study entry not described)	
Interventions	Intravenous monoclonal antibody (oregovomab - CA125)	
Outcomes	Survival (overall survival) Immune responses: humoral (Ab2, Ab3, HAMA)	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Ströhlein 2009

Methods	Uncontrolled phase I study
Participants	9 patients with progressive peritoneal carcinomatosis (ovarian cancer n = 2)
Interventions	Intraperitoneal trifunctional antibody targeting EpCAM (n = 1) or Her2/Neu (n = 1)
Outcomes	Survival: not reported separately for ovarian cancer patients Tumour responses Immune responses: cellular, humoral (HAMA)

Ströhlein 2009 (*Continued*)

	Adverse events	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Takeuchi 2013

Methods	Uncontrolled phase I/II study	
Participants	38 ovarian cancer patients with advanced/recurrent disease	
Interventions	Subcutaneous peptide cocktail (HLA-A24 - n = 23: FOXM1, MELK, HJURP, VEGFR1, VEGFR2; HLA-A02 - n = 13: HIG2, VEGFR1, VEGFR2) Adjuvant: Montanide ISA-51	
Outcomes	Survival Tumour responses Immune responses (not adequately reported) Adverse events (not adequately reported)	
Notes	meeting abstract	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Tsuda 2004

Methods	Uncontrolled phase I/II study
Participants	14 patients with gynaecological cancer after primary therapy (ovarian cancer n = 5; NED n = 2)

Tsuda 2004 (*Continued*)

Interventions	Subcutaneous individualised short peptide cocktail Adjuvant: Montanide ISA-51
Outcomes	Tumour responses Immune responses: humoral, cellular Adverse events: not separately described for ovarian cancer patients
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

van Zanten-Przybysz 2002

Methods	Uncontrolled phase I/II study
Participants	5 patients with residual or recurrent ovarian cancer after primary debulking surgery and at least one course of chemotherapy
Interventions	Intravenous monoclonal antibody (c-MOv18 - membrane folate receptor)
Outcomes	Survival: median time first dose to death 22.0 months Tumour responses: 3x PD, 2x SD Immune responses: cellular Adverse events: max. grade I events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Vermeij 2012

Methods	Uncontrolled phase II study
Participants	12 women with epithelial ovarian cancer with (biochemical) recurrence not (yet) eligible for renewed chemotherapy
Interventions	Subcutaneous synthetic long peptides (p53) Adjuvant: Montanide ISA51 Immunomodulation: cyclophosphamide 2 days prior to each vaccination
Outcomes	Tumour responses Immunological responses: cellular Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial
Allocation concealment (selection bias)	High risk	Uncontrolled trial

Wagner 1993

Methods	Retrospective uncontrolled study
Participants	58 patients with advanced stage ovarian cancer after primary treatment with high pre-operative CA-125 levels (disease status at study entry not described)
Interventions	Intravenous monoclonal antibody fragments ($F(Ab)_2$-fragements of MAb OC125 - CA125)
Outcomes	Survival Tumour responses Immune responses: humoral (Ab2), cellular
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled trial

Wagner 1993 (*Continued*)

Allocation concealment (selection bias)	High risk	Uncontrolled trial

GM-CSF: Granulocyte-macrophage colony-stimulating factor
HAMA: human-anti-mouse antibodies
KLH: keyhole limpet haemocyanin
NED: no evidence of disease

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 2000	Only one woman with EOC, no ASAI
Bender 2007	Only one woman with EOC
Bernal 2012	Only one woman with EOC, no ASAI
Carbone 2005	Only one woman with EOC
Disis 1999	Impossible to distinguish between other and women with ovarian cancer
Disis 2000	Impossible to distinguish between other and women with ovarian cancer
Disis 2002	Impossible to distinguish between other and women with ovarian cancer
Disis 2002a	Only one woman with EOC
Disis 2004	Impossible to distinguish between other and women with ovarian cancer
Disis 2004a	Only one woman with EOC
Galanis 2013	No ASAI
Haakenstad 2012	Impossible to distinguish between other and women with ovarian cancer
Hasumi 2011	No ASAI
Hernando 2002	Autologous tumour lysate vaccine
Hernando 2007	Only one woman with EOC
Holmberg 2000	Impossible to distinguish between breast & women with ovarian cancer participants

(*Continued*)

Hui 1997	No ASAI
Jager 2006	Only one woman with EOC
Kandalaft 2010	Autologous tumour lysate vaccine
Karbach 2010	Only one woman with EOC
Kato 2010	Impossible to distinguish between other and women with ovarian cancer
Khranovska 2011	Autologous tumour lysate vaccine
Knutson 2001	Only one woman with EOC
Knutson 2002	Women with EOC withdrew before evaluation of immune responses
Letsch 2008	Impossible to distinguish between other and women with ovarian cancer
Loveland 2006	Only one woman with EOC
Manjunath 2012	Only one woman with EOC
Marshall 2005	Only one woman with ovarian cancer
Miotti 1999	Autologous T-cell vaccine
Morse 1999	Impossible to distinguish between other and women with ovarian cancer
Morse 2003	Uncertain if and how many women with ovarian cancer were included
Morse 2011a	Impossible to distinguish between other and women with ovarian cancer; unclear number of women with ovarian cancer
Murray 2002	Only one woman with EOC
Parkhurst 2004	No women with EOC
Reddish 1996	Impossible to distinguish between other and women with ovarian cancer
Salazar 2006	Impossible to distinguish between other and women with ovarian cancer
Schiffman 2002	No immunisations carries out
Yacyshyn 1995	Additional results to MacLean 1992; irrelevant for review
Zaks 1998	Impossible to distinguish between other and women with ovarian cancer

ASAI: antigen-specific active immunotherapy
EOC: epithelial ovarian cancer

Characteristics of ongoing studies *[ordered by study ID]*

NCT00003002

Trial name or title	Her-2/neu vaccine plus GM-CSF in treating participants with stage III or stage IV breast, ovarian, or non-small cell lung cancer
Methods	Uncontrolled phase I
Participants	Participants with stage III or IV HER-2/neu expressing breast, ovarian, or non-small cell lung cancer
Interventions	Intradermal vaccinations of HER-2/neu derived peptides with sargramostim (GM-CSF)
Outcomes	Immune responses Adverse events
Starting date	April 1996
Contact information	
Notes	Completed January 2004, no publication available

NCT00004604

Trial name or title	Biological therapy in treating patients with metastatic cancer
Methods	Uncontrolled phase I
Participants	24 participants with histologically confirmed metastatic adenocarcinoma expressing carcinoembryonic antigen (CEA) that has failed conventional therapy
Interventions	Intravenous CEA RNA-pulsed autologous DC
Outcomes	Adverse events Immune responses Clinical and biochemical response
Starting date	February 1998
Contact information	
Notes	Completed July 2002, no publication available

NCT00006041

Trial name or title	Vaccine therapy in treating patients with ovarian, fallopian tube, or peritoneal cancer
Methods	Uncontrolled phase I
Participants	18 participants with histologically confirmed ovarian, fallopian tube, or peritoneal epithelial cancer (any stage at diagnosis). Refractory or recurrent after cytoreductive surgery and at least one prior regimen of platinum based chemotherapy
Interventions	Glycosylated MUC-1-KLH vaccine plus QS21
Outcomes	Adverse events Immune responses
Starting date	February 2000
Contact information	
Notes	Completed February 2002, no publication available

NCT00091000

Trial name or title	An open label pilot study to evaluate the safety and tolerability of PANVAC-V (Vaccinia) and PANVAC-F (Fowlpox) in combination with sargramostim in adults with metastatic carcinoma
Methods	Phase II
Participants	51 participants with histologically confirmed colorectal, non-colorectal, ovarian, or breast carcinoma with evidence of disease
Interventions	sc recombinant vaccinia-CEA-MUC-1-TRICOM vaccine subcutaneously (prime), and sc recombinant fowlpox-CEA-MUC-1-TRICOM vaccine (boost) adjuvant: sc GM-CSF
Outcomes	Safety Clinical responses Immune responses
Starting date	July 2004
Contact information	
Notes	

NCT00373217

Trial name or title	Evaluation of the immunogenicity of vaccination with synthetic peptides in adjuvant in patients with advanced ovarian, primary peritoneal, or fallopian tube cancer
Methods	Phase II study
Participants	28 primary stage III/IV women with ovarian cancer
Interventions	Neoadjuvant paclitaxel/carboplatin followed by surgical debulking, vaccine therapy*, adjuvant paclitaxel/carboplatin or, surgical debulking, vaccine therapy*, followed by adjuvant paclitaxel/carboplatin *id & sc synthetic peptides, (MAGE-A1:161-169, FBP:1901-199, Her-2/neu:369-377, MAGE-A1:96-104, and Her-2/neu:754-762) and tetanus toxoid helper peptide adjuvant: Montanide ISA-51
Outcomes	Immune responses
Starting date	April 2006
Contact information	
Notes	

NCT00381173

Trial name or title	A phase 1 open-label study of the safety and feasibility of ZYC300 administration with cyclophosphamide pre-dosing
Methods	Phase I
Participants	22 advanced stage malignancies with evidence of disease and no therapeutic options
Interventions	im ZYC300 (a plasmid DNA formulated within biodegradable microencapsulated particles) with iv cyclophosphamide
Outcomes	Safety Immune responses Tumour responses
Starting date	November 2006
Contact information	
Notes	Study completion January 2009. No published records available

NCT00803569

Trial name or title	Phase I study of ALVAC(2)-NY-ESO-1(M)/TRICOM in patients with epithelial ovarian, fallopian tube or primary peritoneal carcinoma whose tumors express NY-ESO-1 or LAGE-1 antigen
Methods	Phase I
Participants	12 stage II-IV women with ovarian cancer with complete response to primary or secondary (chemo)therapy
Interventions	sc ALVAC(2)-NY-ESO-1(M)/TRICOM vaccine plus sc GM-CSF
Outcomes	Safety Tumour responses Immune responses
Starting date	November 2008
Contact information	
Notes	

NCT00857545

Trial name or title	A phase III randomized, double-blind trial of a polyvalent vaccine-KLH conjugate (NSC 748933) + OPT-821 Versus OPT-821 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer who are in second or third complete remission
Methods	Randomised phase III study
Participants	164 stage II-IV woman with ovarian cancer in second or third clinical remission
Interventions	sc polyvalent antigen-KLH conjugate vaccine and sc immunological adjuvant OPT-821, or sc OPT-821
Outcomes	Survival Safety Immune responses
Starting date	January 2009
Contact information	
Notes	Possibly same study as NCT00693342

NCT00887016

Trial name or title	Open label phase I study to evaluate the safety and tolerability of vaccine (GI-6207) consisting of whole, heat-killed recombinant saccharomyces cerevisiae genetically modified to express CEA protein in adults with metastatic CEA-expressing carcinoma
Methods	Phase I study
Participants	28 CEA-overexpressing cancer participants without therapeutic options
Interventions	Whole, heat-killed recombinant saccharomyces cerevisiae genetically modified to express CEA protein
Outcomes	Safety Immune responses Clinical responses Survival
Starting date	March 2009
Contact information	
Notes	

NCT00887796

Trial name or title	A phase I clinical trial of NY-ESO-1 protein immunization in combination with 5-AZA-2'-deoxycytidine (decitabine) in patients receiving liposomal doxorubicin for recurrent epithelial ovarian or primary peritoneal carcinoma
Methods	Phase I
Participants	18 women with ovarian cancer with recurrent disease
Interventions	Decitabine in combination with NY-ESO-1 peptide vaccine (emulsified with incomplete Freund's adjuvant and sargramostim [GM-CSF]) and pegylated liposomal doxorubicin hydrochloride
Outcomes	Toxicity Immune responses Survival
Starting date	April 2009
Contact information	
Notes	

NCT00948961

Trial name or title	A study of CDX-1401 in patients with malignancies known to express NY-ESO-1
Methods	Uncontrolled phase I/II dose escalation
Participants	70 participants with a NY-ESO-1 expressing cancer type with progression after prior therapies with curative potential or approved salvage therapies
Interventions	Intradermal injection of CDX-1401 in combination with topical resiquimod and/or intradermal poly-ICLC
Outcomes	Adverse events Clinical responses Survival
Starting date	September 2009
Contact information	
Notes	Completed February 2014

NCT01223235

Trial name or title	Polyvalent vaccine-KLH conjugate + Opt-821 given in combination with bevacizumab
Methods	Uncontrolled phase I
Participants	22 participants who have recently completed chemotherapy and/or surgery for recurrent disease epithelial carcinoma arising from the ovary, fallopian tube or peritoneum
Interventions	Bevacizumab and polyvalent vaccine KLH-conjugate + OPT-821
Outcomes	Adverse events Immune responses Survival
Starting date	October 2010
Contact information	
Notes	

NCT01248273

Trial name or title	Unimolecular pentavalent (GloboH-GM2-sTn-TF-Tn) immunization of patients with epithelial ovarian, fallopian, tube, or peritoneal cancer in first remission
Methods	Uncontrolled phase I

NCT01248273 (*Continued*)

Participants	24 participants in first complete remission after cytoreductive surgery and platinum-based chemotherapy for epithelial carcinoma arising in the ovary, fallopian tube or peritoneum
Interventions	Subcutaneous injection of GloboH-GM2-sTn-TF-Tn conjugate + immunological adjuvant QS-21
Outcomes	Adverse events Immune responses Survival
Starting date	November 2010
Contact information	
Notes	

NCT01322802

Trial name or title	Vaccine therapy in treating patients with stage III-IV or recurrent ovarian cancer
Methods	Uncontrolled phase I
Participants	22 participants with advanced stage or recurrent ovarian cancer treated to complete remission with standard therapies
Interventions	pUMVC3-hIGFBP-2 multi-epitope plasmid DNA vaccine
Outcomes	Adverse events Immune responses Survival
Starting date	March 2012
Contact information	
Notes	

NCT01334047

Trial name or title	Trial of vaccine therapy in recurrent platinum sensitive ovarian cancer patients
Methods	Uncontrolled phase I/II
Participants	20 women with epithelial ovarian cancer with relapse and platinum-sensitive cancer responding to chemotherapy
Interventions	Intradermal immunization with dendritic cells loaded with amplified ovarian cancer stem cell mRNA, hTERT and Survivin

NCT01334047 (*Continued*)

Outcomes	Adverse events Immune responses Survival Clinical Responses
Starting date	April 2011
Contact information	
Notes	

NCT01376505

Trial name or title	Vaccine therapy in treating patients with metastatic solid tumours
Methods	Uncontrolled phase I
Participants	36 participants with an incurable metastatic solid tumour
Interventions	Intramuscular injections with Her-2 vaccine containing two peptides emulsified with nor-MDP in ISA 720 vehicle
Outcomes	Adverse events Immune responses Clinical responses
Starting date	June 2011
Contact information	
Notes	

NCT01522820

Trial name or title	Vaccine therapy with or without sirolimus in treating patients with NY-ESO-1 expressing solid tumours
Methods	Uncontrolled phase 1
Participants	30 participants with solid NY-ESO-1 or LAGE-1 expressing tumours at high risk of recurrence or with minimal residual disease
Interventions	intranodal injections with DEC-205-NY-ESO-1 fusion protein vaccine with or without oral sirolimus
Outcomes	Adverse events Immune responses Survival

NCT01522820 (*Continued*)

Starting date	March 2012
Contact information	
Notes	

NCT01536054

Trial name or title	Sirolimus and vaccine therapy in treating patients with stage II-IV ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer
Methods	Uncontrolled phase I
Participants	12 women with completed therapy for primary or recurrent disease with asymptomatic residual disease or complete remission
Interventions	Subcutaneous injections with ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine, subcutaneous GM-CSF and oral sirolimus
Outcomes	Adverse events Immune responses Survival
Starting date	August 2012
Contact information	
Notes	

NCT01580696

Trial name or title	Phase I/IIa trial of folate binding protein vaccine in ovarian cancer
Methods	Uncontrolled phase I/IIa
Participants	60 women with ovarian, endometrial, fallopian and peritoneal cancer after completion of first line therapy with no evidence of disease at inclusion
Interventions	Intradermal injection with E39 peptide / GM-CSF vaccine
Outcomes	Adverse events Survival
Starting date	April 2012
Contact information	

NCT01580696 (*Continued*)

Notes	

NCT01584115

Trial name or title	Clinical trial of therapeutic vaccine with NY-ESO-1 in combination with the adjuvant monophosphoryl lipid A (MPLA)
Methods	Uncontrolled phase I/II
Participants	15 participants with a NY-ESO-1 expressing malignancy after standard treatment
Interventions	Intramuscular injection with NY-ESO-1 combined with MPLA vaccine
Outcomes	Adverse events Immune responses
Starting date	July 2012
Contact information	
Notes	

NCT01606241

Trial name or title	Cyclophosphamide and vaccine therapy in treating patients with stage II-III breast, ovarian, primary peritoneal, or fallopian tube cancer
Methods	Uncontrolled phase I
Participants	24 women in complete remission after systemic treatment of breast, ovarian, primary peritoneal of fallopian tube cancer
Interventions	Oral cyclophosphamide and intradermal multi-epitope folate receptor alpha peptide vaccine
Outcomes	Adverse events Immune responses
Starting date	July 2012
Contact information	
Notes	

NCT01616303

Trial name or title	A controlled study of effectiveness of oregovomab (antibody) plus chemotherapy in advanced ovarian cancer
Methods	Randomised open label phase II
Participants	80 women with newly diagnosed ovarian, tubal or peritoneal cancer after optimal cytoreductive surgery about to start first-line chemotherapy
Interventions	Carboplatin + paclitaxel vs carboplatin + paclitaxel + oregovomab
Outcomes	Adverse events Immune responses Survival Clinical responses
Starting date	June 2012
Contact information	
Notes	

NCT01621542

Trial name or title	Clinical study of WT2725 in patients with advanced solid malignancies
Methods	Uncontrolled phase I
Participants	80 participants with measurable WT1 expressing advanced stage malignancies
Interventions	WT2725 injection
Outcomes	Adverse events Immune responses
Starting date	July 2012
Contact information	
Notes	

NCT01639885

Trial name or title	Chemo-immunotherapy (gemcitabine, interferon-alpha and p53 SLP) in patients with platinum resistant ovarian cancer (CHIP)
Methods	Non-randomised study

NCT01639885 (*Continued*)

Participants	15 women with recurrent ovarian cancer, peritoneal cavity or fallopian tube cancer overexpressing p53 with disease progression or relapse after previous platinum-based therapy
Interventions	Standard care (gemcitabine) vs gemcitabine combined with interferon-alpha 2b vs gemcitabine combined with interferon-alpha 2b and subcutaneously administered p53-SLP vaccine
Outcomes	Adverse events Immune responses Survival Clinical responses
Starting date	August 2011
Contact information	
Notes	

NCT01673217

Trial name or title	Decitabine, vaccine therapy, and pegylated liposomal doxorubicin hydrochloride in treating patients with recurrent ovarian epithelial cancer, fallopian tube cancer, or peritoneal cancer
Methods	Uncontrolled phase I
Participants	18 women with relapsed epithelial ovarian, fallopian tube or primary peritoneal cancer who are to receive liposomal doxorubicin as salvage therapy for recurrent disease
Interventions	intravenous decitabine, intravenous liposomal doxorubicin, subcutaneous NY-ESO-1 peptide vaccine in Montanide ISA-51, subcutaneous GM-CSF
Outcomes	Adverse events Immune responses Survival
Starting date	April 2009
Contact information	
Notes	study completed June 2013, no publication available

GM-CSF: Granulocyte-macrophage colony-stimulating factor

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Study Report Quality Assessment for non-randomised, non-controlled studies

Item	Question	Evaluation
1. a. b. c.	**Sample Definition and Selection** Are the inclusion and exclusion criteria clearly defined? Is the study population a representative selection of the true population? Are baseline characteristics adequately described?	Yes No ? Yes No ? Yes No ?
2 a. b.	**Interventions** Are the interventions clearly defined (type of vaccine, antigen, adjuvant, route of vaccination and vaccination schedule)? Did patients receive concurrent / concomitant treatment with immunomodulatory effects?	Yes No ? Yes No ?
3 a. b. c.	**Outcomes** Are the selected outcome measures clearly specified? Are the outcome measures relevant? Are the outcome measures clearly reported?	Yes No ? Yes No ? Yes No ?
4. a. b. c.	**Statistical Analysis** Is there an adequate rationale for the number of patients included? Is there an adequate description of withdrawal / exclusion of patients during the study? Is the presentation of the results adequate?	Yes No ? Yes No ? Yes No ?

Table 2. Overview of included studies

Study	Design	N	Disease status	Target antigen	Type of intervention
Baumann 2011	RCT	45	ED after first- and/or second line chemotherapy	EpCAM	antibody (low dose vs high dose)
Berek 2001	RCT	252	NED after primary surgery and chemotherapy	CA-125	antibody versus placebo
Berek 2004	RCT	145	NED after primary surgery and chemotherapy	CA-125	antibody versus placebo

Table 2. Overview of included studies (*Continued*)

Berek 2009	RCT	317	NED after primary surgery and chemotherapy	CA-125	antibody versus placebo
Berinstein 2012	uncontrolled phase I	6	NED or ED after primary surgery	topoisomerase IIα, Integrin β8 subunit precursor, ABI- binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31	short peptides
Berinstein 2013	uncontrolled phase I	19	unknown	survivin	short peptides
Braly 2009	RCT	40	NED or ED after primary surgery	CA-125	antibody (concurrent or delayed with standard chemotherapy)
Brossart 2000	uncontrolled phase I/II	3	residual or recurrent disease	Her-2/Neu or MUC-1	peptide-pulsed dendritic cells
Chianese-Bullock 2008	uncontrolled phase I	9	NED / ED or recurrence after primary therapy	FBP, Her-2/Neu, MAGE-A1	multi-peptide vaccine
Chu 2012	RCT	11	NED after primary therapy or surgery for first recurrence	Her-2/Neu, hTERT, PADRE	peptide-pulsed dendritic cells (with versus without cyclophosphamide)
Dhodapkar 2012	uncontrolled phase I	6	unknown	NY-ESO-1	fusion protein
Diefenbach 2008	uncontrolled phase I	9	NED after primary surgery and chemotherapy	NY-ESO-1	short peptide
Ehlen 2005	uncontrolled phase II	13	measurable recurrent disease	CA-125	antibody
Freedman 1998	RCT	30	unknown	Sialyl-Tn	KLH conjugate (low dose versus high dose)
Galanis 2010	uncontrolled phase I	21	persistent, recurrent or progressive disease after primary therapy	CEA	recombinant virus
Goh 2013	RCT	63	NED after first- or second line therapy	MUC1	protein-pulsed dendritic cells versus standard of care

Table 2. Overview of included studies (*Continued*)

Gordon 2004	uncontrolled phase II	20	recurrent disease	CA-125	antibody
Gribben 2005	uncontrolled phase I	6	ED	CYP1B1	plasmid DNA
Gulley 2008	uncontrolled phase I/II	3	progressive disease after standard chemotherapy	CEA, MUC1	recombinant virus
Heiss 2010	RCT	129	recurrent malignant ascites	EpCAM	antibody + paracentesis vs paracentesis
Imhof 2013	uncontrolled phase I	15	NED after primary therapy	TERT, survivin	mRNA- and peptide-pulsed dendritic cells
Kaumaya 2009	uncontrolled phase I	5	ED after prior therapy	Her2/neu	long peptides
Le 2012	uncontrolled phase I	2	ED after prior therapy	mesothelin	recombinant bacteria
Leffers 2009a	uncontrolled phase II	20	recurrent disease	p53	long peptides
Letsch 2011	uncontrolled	8	unknown	WT1	short peptide
Ma 2002	uncontrolled	4	unknown	CA-125	antibody
MacLean 1992	uncontrolled phase I	10	residual or recurrent disease	Thomson Friedenreich	KLH conjugate
MacLean 1996	uncontrolled phase II	34	residual or recurrent disease	Sialyl-Tn	KLH conjugate
Method 2002	RCT	102	unknown	CA-125	antibody (2 vs 3 vs 6 gifts)
Möbus 2003	retrospective uncontrolled	44	recurrent disease after primary therapy	CA-125	antibody
Mohebtash 2011	uncontrolled	14	recurrent or residual disease after therapy	CEA, MUC1	recombinant virus
Morse 2011	uncontrolled phase I	8	NED after first- or second line chemotherapy	APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I, topoisomerase IIα/β, integrin β 8 subunit pre-	short peptides

Table 2. Overview of included studies (*Continued*)

				cursor, CDC2, TACE, g-catenin, EEDDR1	
Nicholson 2004	uncontrolled phase I	26	residual disease after primary therapy or 2nd complete remission	MUC1	antibody
Nishikawa 2006	uncontrolled phase II	4	unknown	NY-ESO-1	short peptide
Noujaim 2001	retrospective uncontrolled	184	recurrent disease	CA-125	antibody
Odunsi 2007	uncontrolled phase I	18	NED or ED after chemotherapy for primary or recurrent disease	NY-ESO-1	short peptide
Odunsi 2012	uncontrolled phase I/II	22	NED after primary therapy	NY-ESO-1	recombinant virus
Ohno 2009	uncontrolled phase II	6	unknown	WT1	short peptide
Peethambaram 2009	uncontrolled phase I	4	progressive disease after therapy	Her-2/neu	fusion protein pulsed antigen presenting cells
Pfisterer 2006	uncontrolled phase I	36	unknown	CA-125	antibody
Rahma 2012	uncontrolled phase II	21	NED	p53	short peptide versus peptide-pulsed dendritic cells
Reinartz 2004	uncontrolled phase Ib/II	119	unknown	CA-125	antibody
Sabbatini 2000	uncontrolled phase I	25	NED after chemotherapy for primary or recurrent disease	MUC1	KLH conjugate
Sabbatini 2006	RCT	42	NED or ED (<2cm) after chemotherapy for recurrent disease	CA-125	antibody (intramuscular versus subcutaneous)
Sabbatini 2007	uncontrolled phase I/II	11	NED after chemotherapy for primary or recurrent disease	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c), sTN (c), TF(c)	heptavalent KLH conjugate
Sabbatini 2012	uncontrolled phase I	28	NED after second- or third line therapy	NY-ESO-1	long peptides

Table 2. Overview of included studies (*Continued*)

Sabbatini 2013	RCT	888	NED after primary therapy	CA-125	antibody versus placebo
Sandmaier 1999	uncontrolled phase II	7	unknown	Sialyl-Tn	KLH conjugate
Schultes 1998	retrospective uncontrolled	75	unknown	CA-125	antibody
Ströhlein 2009	uncontrolled phase I	2	progressive disease	EpCAM or Her-2/Neu	trifunctional antibody
Takeuchi 2013	uncontrolled phase I/II	38	unknown	HLA-A24: FOXM1, MELK, HJURP, VEGFR1, VEGFR2; HLA-A02: HIG2, VEGFR1, VEGFR2	short peptides
Tsuda 2004	uncontrolled phase I/II	7	NED or ED	patient-tailored cocktail	multi-peptide vaccine
van Zanten-Przybysz 2002	uncontrolled phase I/II	5	residual or recurrent disease after prior chemotherapy	membrane folate receptor	antibody
Vermeij 2012	uncontrolled phase II	12	recurrent disease	p53	long peptides
Wagner 1993	retrospective uncontrolled	58	unknown	CA-125	antibody

Table 3. Assessment of study report quality of non-randomised (un)controlled studies

	N	Clear definition of inclusion/ exclusion criteria	Representative of true population	Baseline characteristics adequately described	Interventions clearly described	Concomitant / concurrent immunomodulatory treatment	Outcome measures clearly specified	Outcome measures relevant	Outcome measures clearly reported	Adequate rationale for number of patients	Adequate description of exclusion / withdrawal	Adequate presentation of results
Berinstein 2012	6	no	unknown	yes	yes	unknown	yes	yes	yes	no	no	yes

Table 3. Assessment of study report quality of non-randomised (un)controlled studies (*Continued*)

Berinstein 2013	19	yes[a]	unknown	no	yes*	yes	no	yes	no	no	no	no
Brossart 2000	3	yes	unknown	no	yes	unknown	yes	yes	yes	no	no	no
Chianese-Bullock 2008	9	yes	no	yes	yes	unknown	yes	yes	yes	no	yes	no
Dhodapkar 2012	6	no	unknown	no	no	unknown	no	yes	no	unknown	no	no
Diefenbach 2008	9	yes	no	yes	yes	no	yes	yes	yes	no	yes	yes
Ehlen 2005	13	yes	yes	yes	yes	unknown	yes	yes	yes	no	yes	yes
Galanis 2010	21	yes	unknown	no	yes	no	yes	yes	yes	no	yes	yes
Goh 2013	63	yes[a]	unknown	no	no	no	no	yes	no	no	no	no
Gribben 2005	6	no	no	no	yes	unknown	no	yes	no	yes	yes	no
Gulley 2008	3	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	no
Imhof 2013	15	yes[a]	unknown	no	yes	no	no	yes	no	no	no	no
Kaumaya 2009	5	no	no	no	yes	no	yes	yes	yes	no	no	no
Le 2012	2	yes	no	no	yes	no	yes	yes	yes	no	no	no
Leffers 2009a	20	yes	unknown	yes	yes	no	yes	yes	yes	yes	yes	yes

Table 3. Assessment of study report quality of non-randomised (un)controlled studies (*Continued*)

Letsch 2011	8	unknown	unknown	no	yes	unknown	unknown	unknown	unknown	unknown	unknown	unknown
Ma 2002	4	no	unknown	no	no	unknown	no	no	no	no	no	no
MacLean 1992	10	no	unknown	no	yes	yes	yes	yes	yes	no	no	yes
MacLean 1996	34	yes	unknown	no	yes	yes	no	yes	no	no	yes	no
Möbus 2003	44	yes	yes	yes	yes	yes	no	yes	yes	no	no	yes
Mohebtash 2011	14	yes	unknown	no	yes	no	yes	yes	yes	no	no	no
Morse 2011	8	yes	no	no	yes	unknown	yes	yes	no	no	yes	no
Nicholson 2004	26	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	yes
Nishikaw 2006	4	no	unknown	no	no	unknown	yes	yes	yes	no	no	no
Noujaim 2001	184	yes	yes	yes	no	unknown	yes	yes	yes	no	no	yes
Odunsi 2007	18	no	no	yes	yes	unknown	no	yes	yes	no	unknown	yes
Odunsi 2012	22	no	yes	yes	yes	no	yes	yes	yes	no	no	yes
Ohno 2009	6	no	unknown	no	yes	no	yes	yes	yes	no	yes	yes
Peethambaram 2009	4	yes	unknown	no	yes	no	yes	yes	no	no	no	no

Table 3. Assessment of study report quality of non-randomised (un)controlled studies (*Continued*)

Pfisterer 2006	36	yes	unknown	no	yes	unknown	yes	yes	yes	no	yes	yes
Rahma 2012	21	no	unknown	no	yes	yes	yes	no	no	yes	yes	no
Reinartz 2004	119	yes	unknown	no	yes	no	yes	yes	yes	no	no	yes
Sabbatini 2000	25	yes	yes	yes	yes	unknown	no	yes	yes	no	yes	yes
Sabbatini 2007	11	yes	unknown	yes	yes	unknown	yes	yes	yes	yes	yes	no
Sabbatini 2012	28	yes	no	yes	yes	no	yes	yes	yes	yes	yes	no
Sandmaier 1999	7	yes	unknown	no	yes	no	no	yes	yes	no	yes	yes
Schultes 1998	75	no	unknown	no	yes	unknown	no	yes	yes	no	no	yes
Ströhlein 2009	2	yes	no	no	yes	unknown	yes	yes	yes	no	yes	yes
Takeuchi 2013	38	yes	unknown	no	yes	no	no	yes	no	no	no	no
Tsuda 2004	5	yes	no	no	yes	no	yes	yes	no	no	yes	no
van Zanten-Przybysz 2002	5	yes	no	yes	yes	unknown	yes	yes	yes	no	yes	yes
Vermeij 2012	12	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	no

Table 3. Assessment of study report quality of non-randomised (un)controlled studies (*Continued*)

Wagner 1993	58	no	unknown	no	yes	unknown	no	yes	no	no	no	no

[a] specified in clinical trial register, not in publication

Table 4. Evaluation of clinical responses to immunotherapy

	N	Analysed	Method	CA-125		Tumour		Overall conclusion
				response definition	results	definition for tumour response	results	
Baumann 2011	45	yes	both	GCIG (evaluable patients C1: 7, C2: 3)	C1: 7x , C2: 3x	RECIST	C1: 2x SD, 21x PD C2: 1x PR, 5x SD, 16x PD	C1: 2x SD, 21x PD C2: 1x PR, 5x SD, 16x PD
Berek 2001	252	no						
Berek 2004	145	no						
Berek 2009	371	no						
Berinstein 2012	6	no						
Berinstein 2013	19	no						
Braly 2009	18/22	yes	unknown			unknown		cCR 15x / 18x
Brossart 2000	3	yes	unknown					2x SD, 1x PD
Chianese-Bullock 2008	9	yes	both	unknown		unknown		1x NED, 8x PD
Chu 2012	11	yes	both	unknown		unknown		3x PD, 7x NED
Dhodapkar 2012	6	yes	unknown					not reported

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Diefenbach 2008	9	yes	both	unknown		unknown		not reported
Ehlen 2005	13	yes	both	decrease >15% (); <15% change (=) stable; >15% increase ()	4x , 1x =, 6x	unknown		3x SD, 10x PD
Freedman 1998	30	yes	unknown					18x SD, 10x PD
Galanis 2010	21	yes	both	GCIG	2x , 3x =, 16x ^?	RECIST	14x SD, 7x PD	14x SD, 7x PD
Goh 2013	63	no						
Gordon 2004	20	yes	both	unknown	6x	unknown		2x NED, 2x CR, 1x PR, 1x SD, 9x PD
Gribben 2005	6	yes	unknown					6x PD
Gulley 2008	3	yes	both	unknown		unknown		not reported
Heiss 2010	129	no						
Imhof 2013	15	yes	unknown					not reproted
Kaumaya 2009	5	yes	unknown					2x SD, 3x PD
Le 2012	2	yes	tumour			RECIST	2x PD	2x PD
Leffers 2009a	20	yes	both	GCIG	not reported	RECIST	not reported	2x SD, 18x PD
Letsch 2011	8	yes	unknown					4x SD, 4x PD
Ma 2002	4	no						
MacLean 1992	10	yes	unknown					3x SD, 7x PD
MacLean 1996	34	no						

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Method 2002	102	yes	unknown					not reported
Möbus 2003	44	no						
Mohebtash 2011	14	yes	unknown					1x SD, 11x PD
Morse 2011	8	no						
Nicholson 2004	26	yes	CA-125	unknown				21x PD, 1x SD, 1x l.f.u., 3x unknown
Nishikawa 2006	4	no						
Noujaim 2001	184	no						
Odunsi 2007	18	yes	tumour			unknown		1x CR, 17x unknown
Odunsi 2012	22	no						
Ohno 2009	6	yes	both	unknown	not reported	RECIST	1x SD, 3x PD	1x SD, 4x PD, 1x withdrawal
Peetham-baram 2009	4	yes	tumour			unknown	2x SD, 2x PD	2x SD, 2x PD
Pfisterer 2006	36	no						
Rahma 2012	21	yes	both	unknown	not reported	RECIST	C1: 2x NED, 11x PD C2: 2x NED, 5x PD	C1: 2x NED, 11x PD C2: 2x NED, 5x PD
Reinartz 2004	119	yes	tumour			WHO		not reported
Sabbatini 2000	25	no						

Table 4. Evaluation of clinical responses to immunotherapy (*Continued*)

Sabbatini 2006	42	yes	both	unknown		unknown		12x SD, 21x PD, 9x withdrawal (6x PD)
Sabbatini 2007	11	no						
Sabbatini 2012	28	yes	tumour			RECIST	C1: 1x NED, 3x PD C2:3x NED, 10x PD C3: 2x NED, 9x PD	C1: 1x NED, 3x PD C2:3x NED, 10x PD C3: 2x NED, 9x PD
Sabbatini 2013	888	no						
Sandmaier 1999	7	no						
Schultes 1998	75	no						
Ströhlein 2009	2	yes	both	unknown		unknown		1x PD, 1x PR or SD
Takeuchi 2013	38	yes	tumour			RECIST	1x CR, 2x PR, 10x SD, 9x PD	1x CR, 2x PR, 10x SD, 9x PD
Tsuda 2004	5	yes	both	unknown		WHO		4x PD, 1x SD
van Zanten-Przybysz 2002	5	yes	both	unknown	1x , 1x =, 1x , 2x unknown	unknown	1x NED, 1x SD, 2x PD, 1x unknown	3xPD, 2xSD
Vermeij 2012	12	yes	both	GCIG	7x /=, 3x	RECIST	not reported	2x SD, 8x PD
Wagner 1993	58	yes	CA-125	unknown				not reported

C1 - cohort 1; l.f.u. - lost in follow-up; cCR - complete clinical remission; CR - complete response; PR - partial response; SD - stable disease; PD - progressive disease; NED - no evidence of disease

Table 5. Definitions and results of survival analysis in antigen-specific antibody studies

Study	Analysed	Definition	Results
Baumann 2011	yes	progression free survival/overall survival	Median PFS: low dose 70 days (95% CI 63 to 91), high dose 68 days (95% CI 58 to 77) Median OS: low dose 137 days (95% CI 99 to 218), high dose 185 (95% CI 134 to 472)
Berek 2001	yes	time to relapse	NS: median TTR placebo 11.3, robust HAMA 16.4, and robust Ab2 18.9 months
Berek 2004	yes	time to relapse/overall survival	NS: TTR oregovomab 24.0 vs. placebo 10. 8 months (HR 0.543, 95% CI 0.287 to 1. 025); OS 57.5 oregovomab vs. 48.6 placebo (HR 0.72, 95% C.I. 0.41 to 1.25)
Berek 2009	yes	time to relapse (randomisation to relapse)	NS: median TTR oregovomab 10.3 months vs placebo 12.9 months
Braly 2009	yes	progression free survival	NS: median PFS simultaneous administration 17.9 months vs. delayed administration 16.1 months
Ehlen 2005	yes	time to progression/survival (first dose to death)	TTP median 8.4 weeks (range 2-61 weeks); survival 37 weeks (range 11-110)
Gordon 2004	yes	time to progression/survival (first dose to death)	TTP median 11 weeks (T-cells responders vs non-responders P < 0.0001 HR 0.150, 95% CI 0.006 to 0.168); survival median 70.4 weeks (T-cell responders vs non-responders P < 0.002 HR 0.157, 95% CI 0.009 to 0. 347)
Heiss 2010	yes	puncture free survival (first dose to therapeutic puncture or death)/overall survival (first dose to death)	Median puncture free survival: paclitaxel + catumaxomab 52 days (95%CI 38-62) vs catumaxomab 11 days (95% CI 9 to 20) Median OS: paclitaxel + catumaxomab 110 days (95% CI 70 to 164) vs catumaxomab 81 days (95% CI 68 to 134)
Ma 2002	no		
Method 2002	no		
Möbus 2003	yes	survival (first dose to death)/overall survival (diagnosis to death)	survival median 16.8 months 95% CI 10.3 to 22.6 (Ab3 responders vs non-responders 18.2 vs 13.1, P = 0.0896; HAMA responders vs non-responders 22.6 months vs 7.6 months, P = 0.0016); overall survival me-

Table 5. Definitions and results of survival analysis in antigen-specific antibody studies (*Continued*)

			dian 34.4 months
Nicholson 2004	no		
Noujaim 2001	yes	survival (first dose to death)	median survival & 3-year survival: Ab3 responders vs non-responders 22.9 vs 13.5 months, P = 0.0089 , 38% vs 8%; T-cell responders vs non-responders (n = 16) > 84 vs 13.2 months, P = 0.0202 , 75% vs 0%
Pfisterer 2006	no		
Reinartz 2004	yes	survival (first dose to death)	median survival 19.4 months, Ab3 responders vs non-responders: 23.4 vs 4.9 months, P < 0.0001
Sabbatini 2006	yes	time to progression	TTP: 4 months (95% CI 3-5 months)
Sabbatini 2013	yes	recurrence free survival (randomisation to recurrence)/overall survival (randomisation to death)	median RFS: abagovomab 403 days (95% CI 323 to 414) vs placebo 402 days (95% CI 323 to 487) 2y OS rate: abagovomab 80% (SE 1.71) vs placebo 80% (SE 2.43)
Schultes 1998	yes	overall survival (diagnosis to death)	median OS: robust Ab3 responders vs non-robust responders 49 vs 38 months , P = 0.0029; Ab2 robust vs non-robust responders 30.0 vs 44.0 months, P = 0.0475
Ströhlein 2009	yes	overall survival	not described separately for ovarian cancer patients
van Zanten-Przybysz 2002	yes	survival (first dose to death)	median survival 22.0 months
Wagner 1993	yes	not described	survival robust Ab2 vs non-robust Ab2 responders NS

SE - standard error; RFS - recurrence free survival; OS - overall survival; TTR - time to relapse; PFS - progression free survival; TTP - time to progression; HR - hazard ratio; CI - confidence interval

Table 6. Definitions and results of survival analysis in other antigen-specific immunotherapy studies

Study	Analysed	Definition	Results
Berinstein 2012	yes	time to progression (study day 0 to relapse)	median TTP > 8 months (range 4 - >9)
Berinstein 2013	no		

Table 6. Definitions and results of survival analysis in other antigen-specific immunotherapy studies (*Continued*)

Brossart 2000	no		
Chianese-Bullock 2008	no		
Chu 2012	yes	progression free survival (first vaccination to relapse)/overall survival (first vaccination to death/last follow-up)	3-yr PFS: arm 1 vs arm 2 40% vs 80% (p = 0. 17) 3yr OS: arm 1 vs arm 2 80% vs 100% (p = 1. 00)
Diefenbach 2008	yes	time to progression (last chemo to relapse)	median TTP 13.0 months (95%CI 11.2 - not reached)
Dhodapkar 2012	no		
Freedman 1998	yes	progression free interval; survival	median PFI 4 months (95% CI 1.9 to 7.6); median survival 13.3. months (95% CI 1.5 to 30.8)
Galanis 2010	yes	overall survival	median OS 12.2 months (range 1.3-38.4)
Goh 2013	yes	progression free survival; overall survival	median PFS vaccine vs standard of care 365 days vs 321 days OS: not reported
Gribben 2005	no		
Gulley 2008	yes	progression free survival; overall survival	PFS: 9, 18, 19^{+} months; OS: 6, 19^{+}, 21 months
Imhof 2013	yes	time to progression (first vaccination to relapse)/overall survival (first vaccination to death)	not reported
Kaumaya 2009	no		
Le 2012	no		
Leffers 2009a	yes	disease specific survival (diagnosis to death of ovarian cancer)	median DSS participants vs historical controls 44.0 months vs 47.4 months
Letsch 2011	no		
MacLean 1996	yes	survival (trial entry to death)	median survival 12.7 months
MacLean 1992	no		
Mohebtash 2011	yes	progression free survival/overall survival	median PFS 2 months (range 1-36) median OS 15.5 months (range 1.5-> 57.0)

Table 6. Definitions and results of survival analysis in other antigen-specific immunotherapy studies (*Continued*)

Morse 2011	yes	overall survival	median OS not reached (range 289-1115+ days)
Nishikawa 2006	no		
Odunsi 2007	yes	time to progression (first vaccination to relapse)	median TTP 19.0 months (95% CI 9.0 - not reached)
Odunsi 2012	yes	progression free survival / overall survival	median PFS 21 months (95% CI 16 to 29 months) median OS 48 months (95% CI not estimable)
Ohno 2009	no		
Peethambaram 2009	yes	time to progression	median TTP 14.0 (range 12.1-18.3)
Rahma 2012	yes	progression free survival (date on study to date progression) overall survival (date on study to date death or last follow-up)	median PFS 4.2 vs 8.7 months median OS 40.8 vs 29.6 months
Sabbatini 2000	yes	time to progression (trial entry to relapse)	median TTP 6 months (range 2-17)
Sabbatini 2007	yes	time to progression (first vaccination to relapse)	median TTP 4.2 months (95% CI 2.7 to 8.5)
Sabbatini 2012	yes	time to progression	no differences between cohorts (numbers not reported)
Sandmaier 1999	no		
Takeuchi 2013	yes	overall survival	median OS: HLA-A24 5 months (range 30-623 days), HLA-A02 9 months (range 54-921 days)
Tsuda 2004	no		
Vermeij 2012	no		

TTR - time to relapse; TTP: time to progression; PFI - progression free interval; PFS - progression free survival; DFS - disease free survival; CI - confidence interval; DSS - disease specific survival; OS - overall survival; SQ - subcutaneous; IV - intravenous

Table 7. Definitions and results of anti-idiotypic (Ab2) humoral responses in antigen-specific monoclonal antibody studies

Study	N	Dose	Target antigen	Analysed	Positive if:	% positive	Robust if:	% Robust
Baumann 2011	45	C1:10-10-10-10 ug C2:10-20-50-100 g	EpCAM	no				
Berek 2001	252	2 mg	CA-125	no	> 50 ng/mL	63%	> 100 ng/mL	
Berek 2004	145	2 mg	CA-125	no			> 100 ng/mL	67%
Berek 2009	371	2 mg	CA-125	no	unknown	not reported	unknown	not reported
Braly 2009	40	unknown	CA-125	yes			> 100 ng/mL	94% vs 74%
Ehlen 2005	13	2 mg	CA-125	yes	> 50 ng/mL	45%		
Gordon 2004	20	2 mg	CA-125	yes	> 50 ng/mL		> 100 ng/mL	79%
Heiss 2010	129	10-20-50-150 ug	EpCAM	no				
Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2 mg	CA-125	no			> 100 ng/mL	13% vs 31% vs 67%
Möbus 2003	44	2 mg	CA-125	yes			> 50 ng/mL	77%
Nicholson 2004	26	25 mg	MUC1	yes	unknown	100%		
Noujaim 2001	184	2 mg	CA-125	yes				
Pfisterer 2006	36	2 mg	CA-125	yes				
Reinartz 2004	119	2 mg	CA-125	yes				
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes				
Sabbatini 2013	888	2mg	CA-125	no				

Table 7. Definitions and results of anti-idiotypic (Ab2) humoral responses in antigen-specific monoclonal antibody studies (*Continued*)

Schultes 1998	75	2 mg	CA-125	yes	> 50 ng/mL	64%	> 250 ng/mL	
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her2/Neu	no				
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	no				
Wagner 1993	58	1 mg	CA-125	no	>0 u/l	64%	> 10 u/l	32%

Table 8. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies

Study	N	Dose	Target antigen	Analysed	Positive if:	% positive	Robust if:	% robust
Baumann 2011	45	C1:10-10-10-10 μg C2:10-20-50-100 μg	EpCAM	no				
Berek 2001	252	2 mg	CA-125	no				
Berek 2004	145	2 mg	CA-125	no				
Berek 2009	371	2 mg	CA-125	no				
Braly 2009	40	unknown	CA-125	no				
Ehlen 2005	13	2 mg	CA-125	yes	> 100 ng/mL		> 3x baseline	0%
Gordon 2004	20	2 mg	CA-125	yes	> 100 ng/mL		> 3x baseline	10,5%
Heiss 2010	129	10-20-50-150 μg	EpCAM	no				
Ma 2002	4	unknown	CA-125	no				
Method 2002	102	2 mg	CA-125	no				
Möbus 2003	44	2 mg	CA-125	yes			> 3x baseline	28%

Table 8. Definitions and results of anti-anti-idiotypic (Ab3) humoral responses in antigen-specific antibody studies (*Continued*)

Nicholson 2004	26	25 mg	MUC1	yes	> 0.015 ug/mL	38%		
Noujaim 2001	184	2 mg	CA-125	yes			> 3x baseline	43%
Pfisterer 2006	36	2 mg	CA-125	yes	> 1000 ng/mL	L vs S: 100% vs 100%		
Reinartz 2004	119	2 mg	CA-125	yes	> 1000 u/mL	68%		
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes	> 1000 u/mL	100%		
Sabbatini 2013	888	2 mg	CA-125	yes	unknown	placebo: stable abagovomab: increase		
Schultes 1998	75	2 mg	CA-125	yes	> 200 ng/mL	24%	> 3x baseline	
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her2/Neu	no				
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	no				
Wagner 1993	58	1 mg	CA-125	no				

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies

Study	N	Target antigen(s)	Analysed	Assay	Positive if:	% positive
Berinstein 2012	6	topoisomerase IIα, integrin β8 subunit precursor, ABI- binding protein C3, TACE/ADAM17, junction plakglobin, EDDR1, BAP31	no			
Berinstein 2013	19	survivin	no			

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies (*Continued*)

Brossart 2000	3	Her-2/Neu, MUC1	no			
Chianese-Bullock 2008	9	FBP, Her-2/Neu, MAGE-A1	no			
Chu 2012	11	Her-2/Neu, hTERT, PADRE	no			
Diefenbach 2008	6	NY-ESO-1	yes	unknown	unknown	not reported
Dhodapkar 2012	9	NY-ESO-1	yes	ELISA	>100	0%
Freedman 1998	21	CEA	yes	ELISA	≥2x pretreatment & > mean + 2SD of 10 normal sera	0%
Galanis 2010	63	MUC1	yes	unknown	unknown	0%
Goh 2013	6	CYP1B1	no			
Gribben 2005	3	CEA, MUC1	no			
Gulley 2008	30	Sialyl Tn	no			
Imhof 2013	15	TERT, survivin	no			
Kaumaya 2009	5	Her-2/neu	yes	ELISA	high response: > 0.6 intermediate response: 0.2-0.6	60% high responses, 40% intermediate responses
Le 2012	2	mesothelin	no			
Leffers 2009a	20	p53	yes	unknown	unknown	pre-imm: 40%, post-imm: 45%
Letsch 2011	8	WT1	no			
MacLean 1996	10	Thomson Friedenreich	yes	ELISA	unknown	80% IgA, 90% IgM, 90% IgG, 0% IgE
MacLean 1992	34	Sialyl Tn	yes	ELISA	unknown	96%
Mohebtash 2011	14	MUC1, CEA	no			
Morse 2011	8	APC, HHR6A, BAP31, replication protein	no			

Table 9. Definitions and results of humoral response evaluation in other antigen-specific immunotherapy studies (*Continued*)

		A, Abl-binding protein 3c, cyclin I, toposiomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1				
Nishikawa 2006	4	NY-ESO-1	no			
Odunsi 2007	18	NY-ESO-1	yes	ELISA	unknown	22%
Odunsi 2012	22	NY-ESO-1	yes	ELISA	unknown	50%
Ohno 2009	6	WT1	no			
Peethambaram 2009	4	Her-2/neu	yes	ELISA	unknown	unknown
Rahma 2012	21	p53	no			
Sabbatini 2000	25	Lewis Y	yes	ELISA	unknown	67%
Sabbatini 2007	11	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c) sTN (c), TF(c)	yes	ELISA	negative to ≥ 1:40 or 8-fold increase	89% ≥3 antigens; 22% GM2, 33% Globo-H, 11% Lewis Y, 100% Tn-MUC1, 44% Tn(c), 44% sTN(c), 78% TF(c)
Sabbatini 2012	28	NY-ESO-1	yes	ELISA	≥100	C1: 25%, C2: 46%, C3: 91%
Sandmaier 1999	7	Sialyl Tn	yes	ELISA	≥1:20	100% IgM, 80% IgG
Takeuchi 2013	38	HLA-A24: FOXM1, MELK, HJURP, VEGFR1, VEGFR2 HLA-A02: HIG2, VEGFR1, VEGFR2	no			
Tsuda 2004	5	patient-tailored cocktail	yes	ELISA	unknown	67%
Vermeij 2012	12	p53	no			

C1 - cohort 1

Table 10. Definitions and results of cellular responses in antigen-specific antibody studies

Study	N	Dose	Target antigen	Analysed	Assay	Positive if:	% positive
Baumann 2011	45	C1:10-10-10-10 μg C2: 10-20-50-100 μg	EpCAM	no			
Berek 2001	252	2 mg	CA-125	no			
Berek 2004	145	2 mg	CA-125	no			
Berek 2009	371	2 mg	CA-125	no			
Braly 2009	40	unk	CA-125	yes	ELISPOT	permutation test	44% vs. 21%
Ehlen 2005	13	2 mg	CA-125	yes	ELISPOT	permutation test	n = 4 CA-125: 75%; n = 3 oregovomab 67%
Gordon 2004	20	2 mg	CA-125	yes	ELISPOT	permutation test	n = 18 CA-125: 39%; n = 18 oregovomab 50%; n = 8 autologous tumour cells 63%
Heiss 2010	129	10-20-5-150 μg	EpCAM	no			
Ma 2002	4	unk	CA-125	yes	proliferation assay	unknown	n = 4: 50%
Method 2002	102	2 mg	CA-125	yes	ELISPOT	not reported	not reported
Möbus 2003	44	2 mg	CA-125	no			
Nicholson 2004	26	25 mg	MUC1	no			
Noujaim 2001	184	2 mg	CA-125	yes	proliferation assay/ cytokine ELISA	proliferation assay: wilcoxon signed rank test; cytokine ELISA: unknown	n = 17 CA-125 53%; Th1 cytokines 41%, Th2 cytokines 94%
Pfisterer 2006	36	2 mg	CA-125	yes	cytokine flow cytometry	> 2-fold increase in IFN-γ expressing T-cells	L vs S: n = 12 vs 17, CD4: 58% vs 29%; CD8 75% vs 18%

Table 10. Definitions and results of cellular responses in antigen-specific antibody studies (*Continued*)

Reinartz 2004	119	2 mg	CA-125	no			
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes	ELISPOT	spots experimental wells - control wells > 20 & experimental wells/ control wells > 1. 5x	n = 5: 80%
Sabbatini 2013	888	2 mg	CA-125	yes	not reported		not reported
Schultes 1998	75	2 mg	CA-125	no			
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her2/Neu	yes	IFN-γ secretion assay	unknown	EpCAM n = 1 (100%) Her2/Neu n = 1 (0%)
van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	yes	proliferation assay	unknown	0%
Wagner 1993	58	1 mg	CA-125	yes	leukocyte migration inhibition assay	unknown	21%

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies

Study	N	Target antigen(s)	Analysed	Assay	Positive if:	% positive
Berinstein 2012	6	topoisomerase IIα, integrin β8 subunit precursor, ABI- binding protein C3, TACE/ ADAM17, junction plakglobin, EDDR1, BAP31	yes	pentamer staining (CD8)	> 2x increase of pentamer positive CD8-cells	83% against at least 1 peptide
Berinstein 2013	19	survivin	yes	ELISPOT tetramer staining intracellular cytokine staining	unknown	combined results C2+C3: 92% on $\geq$ 2 assays
Brossart 2000	3	Her-2/Neu, MUC1	yes	intracellular IFN-γ staining (CD8)	unknown	n = 1: Her-2/Neu 100%; n = 2 MUC1 50%

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

Chianese-Bullock 2008	9	FBP, Her-2/Neu, MAGE-A1	yes	ELISPOT (CD8)	unknown	n = 9: FBP 40%, Her-2/neu 83%, MAGE-A1 83%
Chu 2012	14	Her-2/Neu, hTERT, PADRE	yes	ELISPOT tetramer staining (CD8)	unknown	hTERT: C1: 100%, C2: 100% Her-2/Neu: C1: 60%, C2: 0% PADRE: C1 60%, C2: 60%
Diefenbach 2008	6	NY-ESO-1	yes	ELISPOT Intracellular cytokine staining	unknown	not reported
Dhodapkar 2012	9	NY-ESO-1	yes	ELISPOT / Tetramer staining (CD8)	specific spots > 30 and > 3x spots irrelevant control > 0.1% tetramer positive CD8-cells	both assays n = 9: 67%
Freedman 1998	30	Sialyl Tn	no			
Galanis 2010	21	CEA	no			
Goh 2013	63	MUC1	yes	unknown		not reported
Gribben 2005	6	CYP1B1	yes	ELISPOT	spots minus negative control>20 / 10^6 PBMC & >2x baseline	n = 5: 20%
Gulley 2008	3	CEA, MUC1	yes	ELISPOT (CD8) / IFN-γ ELISA (CD4)	ELISPOT: $\geq$2-fold increase in IFN-γ secreting cells IFN-γ ELISA: unknown	n = 3: 100% CEA n = 3: 33% CEA
Imhof 2013	15	TERT, survivin	yes	intracellular cytokine staining	unknown	overall > 90%
Kaumaya 2009	5	Her-2/neu	no			
Le 2012	2	mesothelin	yes	ELISPOT (CD8)	specific spots >2x baseline & $\geq$1 per 10^5 PBMC	n = 1 evaluable, mesothelin specific CD8 cells present

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

Leffers 2009a	20	p53	yes	ELISPOT Proliferation assay Intracellular cytokine staining (CD4/CD8)	- specific spots ≥ 10/10^5 PBMC & ≥ 3x pre-immunization - cpm > 1000/minute, SI≥3 and ≥ 2x pre immunization - ≥3 pre-immunization	n = 18: 100% n = 17: 82% n = 5: CD8 0%, CD4 100%
Letsch 2011	8	WT1	yes	tetramer staining	unknown	not reported
MacLean 1996	10	Sialyl Tn	no			
MacLean 1992	34	Thomson Friedenreich	no			
Mohebtash 2011	14	MUC1, CEA	yes	ELISPOT (CD8)	≥2x pre-immunization	n = 2: 0% MUC1 specific CD8-cells 50% CEA specific CD8-cells
Morse 2011	8	APC, HHR6A, BAP31, replication protein A, Abl-binding protein 3c, cyclin I, toposiomerase IIα/β, integrin β 8 subunit precursor, CDC2, TACE, g-catenin, EEDDR1	yes	ELISPOT	>40 spots / 10^6 PBMC over prevaccination	n = 8: 63%
Nishikawa 2006	4	NY-ESO-1	yes	ELISPOT (CD4)	unknown	n = 4: 75%
Odunsi 2007	18	NY-ESO-1	yes	ELISPOT (CD4/CD8)	mean ± 3 SD	n = 18: CD4 - 83%, CD8 - 33%
Odunsi 2012	22	NY-ESO-1	yes	ELISPOT (CD4/CD8) Intracellular cytokine staining (CD8)	unknown	CD4: 91% CD8: 45%
Ohno 2009	6	WT1	no			
Peethambaram 2009	4	Her-2/neu	yes	proliferation assay ELISPOT assay	unknown	not reported separately for ovarian cancer patients

Table 11. Definitions and results of cellular responses in other antigen-specific immunotherapy studies (*Continued*)

Rahma 2012	21	p53	yes	ELISPOT tetramer staining	≥ 2x pre-immunization	C1: 64%, C2: 83%
Sabbatini 2000	25	Lewis Y	no			
Sabbatini 2007	11	GM2, Globo-H, Lewis Y, Tn-MUC1, Tn(c) sTN (c), TF(c)	no			
Sabbatini 2012	28	NY-ESO-1	yes	ELISPOT (CD4/CD8)	>50 spots / $5x10^4$ cells & >3x unstimulated cells	CD4: 100% in C1/C2/C3 CD8: C1 0%, C2 62%, C3 92%
Sandmaier 1999	7	Sialyl Tn	yes	proliferation assay*	> upper limit of normals (SI 2.35)	n = 4: 50%
Takeuchi 2013	38	HLA-A24: FOXM1, MELK, HJURP, VEGFR1, VEGFR2 HLA-A02: HIG2, VEGFR1, VEGFR2	yes	unknown	unknown	inadequately reported
Tsuda 2004	5	patient-tailored cocktail	yes	IFN-γ ELISA	unclear	n = 2 after 6 vacc. 100%; n = 1 after 12 vacc. 100%
Vermeij 2012	12	p53	yes	ELISPOT proliferation assay	- specific spots ≥ 10/10^5 PBMC & ≥ 3x pre-immunization - cpm > 1000/minute, SI≥3 and ≥ 2x pre immunization	90% after 2 vacc, 87.5% after 4 vacc. 80% after 2 vacc, 62.5% after 4 vacc.

* as measured after at least three immunizations; SI - stimulation index; SD - standard deviation; C1 - cohort 1

Table 12. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies

Study	N	Dose	Target antigen	Analysed	Positive if:	% positive	Robust if:	% robust
Baumann 2011	45	C1:10-10-10-10 μg C2:10-20-50-100 μg	EpCAM	yes	unknown	C1 61%, C2 100%		

Table 12. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies (*Continued*)

Berek 2001	252	2 mg	CA-125	yes			> 5000 ng/mL	51%
Berek 2004	145	2 mg	CA-125	yes	> 200 ng/mL	unknown	> 5000 ng/mL	59%
Berek 2009	371	2 mg	CA-125	yes	unknown	n.r.		
Braly 2009	40	unk	CA-125	yes	unknown	SIM vs OWD: 100% vs 80%	> 3000 ng/mL	SIM vs OWD: 88% vs 74%
Ehlen 2005	13	2 mg	CA-125	yes	> 200 ng/mL	100%	> 5000 ng/mL	58%
Gordon 2004	20	2 mg	CA-125	yes	> 200 ng/mL	unknown	> 5000 ng/mL	79%
Heiss 2010	129	10-20-50-150 μg	EpCAM	yes	unknown	not reported		
Ma 2002	4	unk	CA-125	no				
Method 2002	102	2 mg	CA-125	yes	> 200 ng/mL	unknown	unknown	4% vs 36% vs 39%
Möbus 2003	44	2 mg	CA-125	yes			> 5000 ng/mL	68%
Nicholson 2004	26	25 mg	MUC1	no				
Noujaim 2001	184	2 mg	CA-125	no				
Pfisterer 2006	36	2 mg	CA-125	yes	> 15 ng/mL	L vs. S: 94% vs 100%		
Reinartz 2004	119	2 mg	CA-125	yes	> 100 ng/mL	78%		
Sabbatini 2006	42	2 mg/0.2 mg	CA-125	yes	> 100 ng/mL	90%		
Sabbatini 2013	888	2 mg	CA-125	yes	unknown	inadequately reported		
Schultes 1998	75	2 mg	CA-125	yes	> 200 ng/mL	90%		
Ströhlein 2009	2	10/20/40 μg 10/40/80 μg	EpCAM Her2/Neu	yes	unknown	100% (n = 1)		

Table 12. Definitions and results of human-anti-mouse antibody (HAMA) evaluation in antigen-specific antibody studies (*Continued*)

van Zanten-Przybysz 2002	5	50 mg	membrane folate receptor	n.a.				
Wagner 1993	58	1 mg	CA-125	no				

n.a. - not applicable; n.r. - not reported

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2 ovar* near/5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan*)
#3 #1 or #2
#4 MeSH descriptor: [Immunotherapy, Active] explode all trees
#5 MeSH descriptor: [Cancer Vaccines] explode all trees
#6 immunotherapy or vaccination* or vaccine* or immunization or immunisation
#7 #4 or #5 or #6
#8 MeSH descriptor: [Antigens, Neoplasm] explode all trees
#9 antigen*
#10 #8 or #9
#11 MeSH descriptor: [T-Lymphocytes] explode all trees
#12 (T cell*) or T-cell* or (T lymphocyte*) or T-lymphocyte* or CD4* or CD8*
#13 #11 or #12
#14 #3 and #7 and #10 and #13

Appendix 2. MEDLINE search strategy

MEDLINE Ovid
1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 exp Immunotherapy, Active/
5 Cancer Vaccines/
6 (immunotherapy or vaccination* or vaccine* or immunization or immunisation).mp.
7 4 or 5 or 6
8 exp Antigens, Neoplasm/
9 antigen*.mp.
10 8 or 9
11 exp T-Lymphocytes/
12 (T cell* or T-cell* or T lymphocyte* or T-lymphocyte* or CD4* or CD8*).mp.
13 11 or 12

14 3 and 7 and 10 and 13
key:
mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier

Appendix 3. EMBASE search strategy

EMBASE Ovid
1 exp ovary tumor/
2 (ovar* adj5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 active immunization/
5 cancer vaccine/
6 (immunotherapy or vaccination* or vaccine* or immunization or immunisation).mp.
7 4 or 5 or 6
8 exp tumor antigen/
9 antigen*.mp.
10 8 or 9
11 exp T lymphocyte/
12 (T cell* or T-cell* or T lymphocyte* or T-lymphocyte* or CD4* or CD8*).mp.
13 11 or 12
14 3 and 7 and 10 and 13
key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Appendix 4. Data extraction form

CRITICAL REVIEW & DATA EXTRACTION FORM
Review Title: Antigen-specific active immunotherapy for ovarian cancer
Date: …… Reviewer: ……
Study Title: …….

First Author	
Year of Publication	
Country of Publication	
Publication Type	Journal / Abstract / other (specify)

Study Characteristics*

	Study
Study inclusion criteria	
Study exclusion criteria	
Participants	· Total number of participants: …… · Number of patients with EOC: ……. · Age: o Median + range: …… o Mean + SD: …… · FIGO stage: …… · Histological tumor type: …… · Tumour grade: …… · Previous therapy: …… · Concurrent therapy: ……..
Trial intervention	· type of vaccine: …… · antigen used: …… · adjuvant used: ……. · route of vaccination: …… · vaccination schedule: …….

Outcomes

Trial	N + reason
Patients excluded during trial	
Patients lost to follow-up	

Clinical responses	N
CA-125 levels according to GCIG definition	Decreasing: ……. Stable: …….. Progressing: …… Total: …….
Tumour response according to RECIST or WHO criteria	Complete remission: ……. Partial remission: …….. Stable disease: …….. Progressive disease: …….. Total: …….

(*Continued*)

Postimmunotherapy treatment	Administered: Yes ? No ? If yes: specify response to post immunotherapy treatment: Complete remission: ……. Partial remission: …….. Stable disease: …….. Progressive disease: …….. Total: …….
Survival	Information on survival available: Yes ? No ? If yes, specify: …… ……

Immunogenicity	
1. *Antigen-specific immunogenicity*	
Humoral responses	Observed Total Assay(s) used: ……
Cellular responses	Observed Total Assay(s) used: …… Separate information on cytotoxic T-lymphocytes and Thelper lymphocytes available: Yes ? No ? If yes, specify: ……
Vaccine or vector specific immunogenicity: Applicable Yes ? No ?	
Humoral responses	Observed Total Assay(s) used: ……
Cellular responses	Observed Total Assay(s) used: ……

Adverse events	
Type of AE's	· Local events (injection site): Yes ? No ? If yes, specify: …… · Systemic: Yes ? No ? If yes: Autoimmunity Yes ? No ? If yes, specify: …… Allergic reactions Yes ? No ? If yes, specify: …… Other Yes ? No ? If yes, specify: ……

Other

Contact with primary investigators	Clarify Methods ? Clarify Results ?
Notes	

WHAT'S NEW

Date	Event	Description
8 September 2014	Amended	Author details amended
31 July 2014	New search has been performed	Searches re-run October 2013. New studies included and excluded
10 July 2014	New citation required but conclusions have not changed	The text of the review was updated to reflect additional studies included and excluded. Overall, conclusions unchanged

CONTRIBUTIONS OF AUTHORS

NL selected relevant studies, assessed study quality, extracted data and wrote the review. HWN selected relevant studies, assessed study quality and extracted data. TD and WH checked all rejected titles and resolved any disagreements on study selection and data extraction. HMB and BC provided statistical and methodological support. KM supported in writing the review as an expert in immunology.

DECLARATIONS OF INTEREST

Ninke Leffers, Cornelis Melief, Toos Daemen and Hans Nijman were investigators in two studies included in this review (Leffers 2009a; Vermeij 2012). No potential conflicts of interest exist for the other contributing authors.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

TD was added to the team. For the update of the review, we used The Cochrane Collaboration's Risk of bias' tool to assess the risk of bias in randomised controlled trials, whereas in the protocol and the previous version of the review the Delphi list was used. There are no further relevant differences between protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [adverse effects; therapeutic use]; CA-125 Antigen [immunology]; Clinical Trials, Phase I as Topic; Clinical Trials, Phase II as Topic; Immunotherapy, Active [adverse effects; *methods]; Molecular Targeted Therapy [methods]; Neoplasms, Glandular and Epithelial [immunology; *therapy]; Ovarian Neoplasms [immunology; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans